METALS AND NEUROLOGICAL DISORDERS

EXPLORING NEUROTOXICITY MECHANISMS AND RECEPTOR TARGETS

Editor:
Shamsher Singh

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Metals and Neurological Disorders: Exploring Neurotoxicity Mechanisms and Receptor Targets

Edited by

Shamsher Singh
Neuroscience Division, Department of Pharmacology
ISF College of Pharmacy, Moga, Punjab
India

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Editor: Shamsher Singh

ISBN (Online): 979-8-89881-525-7

ISBN (Print): 979-8-89881-526-4

ISBN (Paperback): 979-8-89881-527-1

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First published in 2026.

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PREFACE

The book "*Metals and Neurological Disorders: Exploring Neurotoxicity Mechanisms and Receptor Targets*" has been written with the intent to provide an in-depth, accessible exploration of how metal exposure affects the human nervous system physiologically and pathologically. This book serves as a multidisciplinary resource that connects the dots between toxicology, neurobiology, pharmacology, and clinical research.

Metal ions are essential for numerous physiological functions, but their imbalance or accumulation in the body can lead to emphasizing neurological consequences. Throughout my academic and research experience, I noticed a lack of comprehensive texts addressing the complex interactions between metals and neural tissues, particularly those that integrate molecular mechanisms, receptor-level interactions, clinical evidence, and translational approaches. This gap served as the driving force behind writing this book. The content of this book is arranged to follow a logical flow: beginning with fundamental aspects of metal homeostasis, moving through exposure pathways and mechanisms of toxicity, and progressing into specific disorders, genetic susceptibility, and diagnostic strategies. Special chapters have been dedicated to metals such as aluminium, lead, and iron, which are frequently implicated in neurodegenerative disorders. Additional focus is placed on biomarkers, neuropsychological assessments, and advanced imaging techniques to support early diagnosis and targeted interventions.

Further, the book explores emerging tools, such as nanotechnology, along with nutritional and lifestyle strategies that may modulate metal-induced neurotoxicity. A dedicated section on clinical trials and translational research offers insights into how benchside findings are being brought into clinical contexts, with an emphasis on future therapeutic avenues. This book is intended for students, academicians, researchers, and healthcare professionals in disciplines such as pharmacy, neuroscience, medicine, toxicology, and biomedical engineering. Each chapter has been written with a focus on simplicity, accuracy, and practical application, supported by well-illustrated diagrams and up-to-date references.

We hope this book contributes meaningfully to the growing field of neurotoxicology and provides a solid foundation for further academic exploration and research. Constructive feedback and suggestions from readers will be deeply appreciated and will guide future editions of this work.

Shamsher Singh
Neuropharmacology Division, Department of Pharmacology
ISF College of Pharmacy, Moga, Punjab
India

List of Contributors

Ajay Bommareddy	Biomedical Science Department, Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida, USA
Ajay Singh Kushwah	Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India
Anil Kumar	Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, India
Balwinder Kaur	Department of Chemistry, Punjabi University, Patiala, Punjab, India
Dhrita Chatterjee	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Dhruva Kumar	Department of Chemistry, Guru Nanak College, Budhlada, Punjab, India
Falguni Goel	Department of Pharmaceutical Technology, Meerut Institute of Engineering & Technology (MIET), Meerut, India
G.D Gupta	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India
Garima Sharma	Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, India
Kamal Preet Mehra	Department of Pharmacology, RIMT University, Sirhind, Mandi Gobindgarh, Punjab, India
Karan Sharma	Department of Pharmacology, Shiva Institute of Pharmacy, Bilaspur, Himachal Pradesh, India
Khadga Raj Aran	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Komal Komal	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India
Kousik Maparu	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Kousik Maparu	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Lav Goyal	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Lovekesh Singh	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Medha Bhalla	Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India
Naga Rani Kagithala	School of Medical & Allied Sciences, Department of Pharmacy, Galgotias University, Greater Noida, Uttar Pradesh, India
Navpreet Kaur	Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab, India
Neelam Sharma	Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy (An Autonomous College), , BELA (Ropar), Punjab, India

Nileshwar Kalia	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Pavittar Singh	Department of Pharmaceutical Analysis, ISF College of Pharmacy, Moga, Punjab, India
Prem Shankar Mishra	School of Medical & Allied Sciences, Department of Pharmacy, Galgotias University, Greater Noida, Uttar Pradesh, India
R.K. Narang	Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India
Rahul Kumar	School of Medical & Allied Sciences, Department of Pharmacy, Galgotias University, Greater Noida, Uttar Pradesh, India
Rahul Kumar Sharma	Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy (An Autonomous College), , BELA (Ropar), Punjab, India
Rajesh Kumar	Department of Chemistry, Govt. Degree College Khundian, District Kangra, HP, India
Ramandeep Kaur	Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab, India
Ramandeep Kaur	Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India
Ravina Kumari	Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India
Ritu Kainth	Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India
Romanpreet Kaur	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
S.K. Abdul Rahaman	School of Medical & Allied Sciences, Department of Pharmacy, Galgotias University, Greater Noida, Uttar Pradesh, India
Sakshi Patel	School of Medical & Allied Sciences, Department of Pharmacy, Galgotias University, Greater Noida, Uttar Pradesh, India
Sanchi Jain	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Sania Grover	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Shamsher Singh	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India
Shilpa Thakur	Department of Pharmacology, Shiva Institute of Pharmacy, Bilaspur, Himachal Pradesh, India
Subhash Chand	Department of Chemistry, Lajpat Rai D.A.V College, Jagraon, Punjab, India
Sudarshan Kumar	Department of Pharmaceutical Analysis, ISF College of Pharmacy, Moga, Punjab, India
Suraj Sharma	Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, India
Tanya Vats	Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India

Vaishali Dobhal	Motherhood University, Roorkee, Uttarakhand, India
Vipin Kumar Garg	Department of Pharmaceutical Technology, Meerut Institute of Engineering & Technology (MIET), Meerut, India
Vivek Asati	Department of Pharmaceutical Analysis, ISF College of Pharmacy, Moga, Punjab, India
Yukti Mittal	Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab, India

CHAPTER 1

Introduction to the Role of Metals and Neurodegenerative Disorders

Dhrita Chatterjee[1], Romanpreet Kaur[1] and **Shamsher Singh[1,*]**

[1] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Neurological disorders encompass a diverse group of conditions that affect the brain, spinal cord, and peripheral nerves. Their pathophysiology is multifactorial, involving genetic mutations, infections, trauma, autoimmune responses, and exposure to environmental toxins. Central to many of these disorders are pathological mechanisms such as neurodegeneration, synaptic dysfunction, neuroinflammation, and abnormal protein aggregation. Increasing evidence highlights the critical role of metal homeostasis, both of essential and toxic metals, in neurological health and disease. Essential metals, such as iron, zinc, copper, and magnesium are crucial for cellular metabolism, neurotransmission, and antioxidant defence. However, their dysregulation, whether through deficiency or overload, can induce oxidative stress and contribute to neurodegenerative processes. Conversely, toxic metals like lead, mercury, cadmium, arsenic, and aluminium pose serious threats to neuronal integrity by mimicking essential metals, disrupting enzymatic function, and triggering inflammation and apoptosis. This chapter explores how the dualistic roles of metals modulate key cellular pathways and influence the onset and progression of neurological diseases. A deeper understanding of metal-mediated neuropathology may offer promising avenues for biomarker discovery and therapeutic intervention.

Keywords: Apoptosis, Biomarker, Neurodegeneration, Neuroinflammation, Oxidative stress.

INTRODUCTION

Neurological disorders encompass a wide range of conditions that affect the nervous system, including the brain, spinal cord, and peripheral nerves. These disorders can result from a variety of causes, such as genetic mutation, infections, autoimmune responses, trauma, and exposure to toxic metals. The pathophysiology of neurological disorders is often complex and multifactorial, involving disruptions to cellular structure, biochemical pathways, and electrical

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

signaling. Common pathological mechanisms underlying many neurological diseases include neurodegeneration, synaptic dysfunction, neuroinflammation, and abnormal protein aggregation. Neurodegenerative diseases like Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS) involve the progressive loss of neurons, leading to cognitive decline, motor dysfunction, and other debilitating symptoms. In Alzheimer's, for example, the accumulation of beta-amyloid plaques and neurofibrillary tangles disrupts neuronal communication, while in Parkinson's, the loss of dopamine-producing neurons leads to motor impairments. Nowadays, metals like aluminium, lead, and mercury are widely exposed in animal models due to their neurodegenerative potential to understand the metal-associated neurological problems. Additionally, synaptic dysfunction, where the connections between neurons are impaired, can disrupt communication across neuronal circuits, leading to a variety of neurological symptoms.

Another critical aspect in the development of neurological disorders is neuroinflammation, which refers to the activation of microglia and astrocytes, immune cells in the brain and spinal cord, in response to injury and disease. This inflammation can exacerbate neuronal damage and contribute to disease progression, particularly in autoimmune disorders such as multiple sclerosis (MS). Moreover, vascular damage, including conditions like stroke, can result in the interruption of blood flow to the brain, leading to neuronal death and significant neurological deficits. Trauma, such as brain and spinal cord injuries, can also cause long-lasting neurological problems by disrupting neuronal circuitry and blood-brain barrier integrity.

In recent years, emerging research has highlighted the critical role of metals, both essential and non-essential, in the pathogenesis of neurological diseases. Metals are involved in a variety of cellular processes, ranging from enzyme catalysis and protein folding to neurotransmitter synthesis and oxidative stress regulation. While essential metals are necessary for normal physiological function, their dysregulation can contribute to the pathogenesis of neurological diseases. Metals play a decisive role in human physiology, being integral to a variety of biochemical processes. Around ten metals are considered essential for life, including sodium (Na^{2+}), potassium (K), magnesium (Mg), calcium (Ca^{2+}), manganese (Mn), iron (Fe), cobalt (Co), zinc (Zn), nickel (Ni), copper (Cu), and molybdenum (Mo). These metals, while essential for life, vary in terms of their quality and biological role. They can be categorized into two groups: nontransition elements (such as Na, K, Mg, and Ca) and transition elements (like Fe, Co, and Cu). Non-transition metals tend to maintain a constant oxidation state and exhibit filled electron shells, while transition metals can exist in multiple oxidation states and have incomplete electron shells, giving them unique physical and chemical properties. For instance, metals like calcium and magnesium are

present in relatively large quantities in the body and contribute to essential functions like bone and tooth structure (Ca^{2+}) and energy production (Mg^{2+}). In contrast, transition metals such as iron, zinc, and copper, though present in trace amounts, are vital for numerous physiological functions such as oxygen transport, antioxidant defence, enzyme catalysis, and protein folding. Iron, for example, is crucial for oxygen binding in hemoglobin, while copper is involved in redox reactions and antioxidant defense. Zinc plays a central role in controlling neurotransmitters' function and synaptic activity, which are crucial for cognition and memory.

Although these metals are essential for normal cellular functioning, any imbalance, whether through deficiency or excess, can lead to significant biological consequences. A deficiency in essential metals like iron or zinc can impair processes like oxygen transport or immune function, contributing to disorders such as anemia or cognitive decline. On the other hand, excessive levels or exposure to metals, such as iron and copper, can result in oxidative stress, leading to cellular damage and diseases, including neurodegeneration. The dynamic interplay between essential metals and the body's biochemical processes underscores the importance of maintaining proper metal homeostasis to prevent diseases. Furthermore, exposure to non-essential metals such as lead, mercury, and cadmium can disrupt cellular function due to their chemical similarity to essential metals, often substituting in key biochemical pathways and impairing normal physiological functions. These toxic metals can bind to proteins, disrupt enzyme activity, and increase oxidative stress, contributing to neuronal injury and promoting the development of neurological disorders. Therefore, understanding the intricate roles of both the essential and toxic metals in cellular processes is crucial for unravelling their contribution to the pathophysiology of neurological and other diseases.

Among these essential metals, Sodium (Na) plays a crucial role in maintaining fluid balance, nerve transmission, and muscle contraction. It is a key component in the sodium-potassium pump (Na^+/K^+-ATPase), which regulates membrane potential and helps in nerve signal transmission. It also influences blood pressure and acid-base homeostasis. Deficiency of sodium can lead to dehydration, confusion, and muscle weakness. Similarly, potassium (K) is essential for maintaining intracellular fluid balance, nerve signaling, and muscle contraction, critical for cardiac function, and regulates blood pressure by counteracting the effects of sodium. Potassium also activates various enzymes involved in metabolism and protein synthesis. Its deficiency can cause muscle cramps, arrhythmias, and weakness.

CHAPTER 2

Metal Homeostasis in the Human Body

Rahul Kumar Sharma[1], Shilpa Thakur[2], Karan Sharma[2], Neelam Sharma[1,*], Tanya Vats[3], G.D. Gupta[4] and **Shamsher Singh[3]**

[1] *Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy (An Autonomous College), BELA (Ropar), Punjab, India*

[2] *Department of Pharmacology, Shiva Institute of Pharmacy, Bilaspur, Himachal Pradesh, India*

[3] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

[4] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Metal homeostasis is essential for maintaining physiological balance and ensuring proper cellular function in the human body. Essential metals such as iron, zinc, copper, calcium, and magnesium play pivotal roles in enzymatic activity, neurotransmission, gene expression, and antioxidant defense. However, even slight disturbances in their regulation can trigger pathological processes, including oxidative stress, mitochondrial dysfunction, and inflammation. The body maintains metal homeostasis through a finely tuned network of transporters, storage proteins, and regulatory pathways that control absorption, distribution, and excretion. Disruption of these mechanisms due to genetic factors, environmental exposure, or disease can lead to serious health outcomes, particularly neurodegenerative disorders. Understanding the intricate mechanisms of metal uptake, trafficking, and cellular compartmentalization is vital for developing targeted diagnostics and therapies. This section delves into the molecular pathways of metal regulation and highlights their significance in health and disease, offering insights into how restoring homeostasis may serve as a therapeutic strategy against metal-induced pathologies.

Keywords: Absorption, Metal homeostasis, Metal transporters, Metal imbalance, Neurotransmission.

INTRODUCTION

Metal homeostasis is the precise control of metal ions in the human body, ensuring vital metals are maintained at optimal levels to support a wide range of physiological functions. Metals such as iron, zinc, copper, manganese, and

* **Corresponding author Neelam Sharma:** Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy (An Autonomous College), BELA (Ropar), Punjab, India; E-mail: pharmneelam@gmail.com

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calcium are essential for energy production, DNA synthesis, immunological response, enzymatic reactions, and many other vital processes. However, having too much of these metals or not enough of them might cause major health issues [1]. The human body must maintain a careful equilibrium by effectively absorbing vital metals from food, delivering them to the tissues where they are required, storing them securely, and eliminating any excess to avoid toxicity [2, 3]. Specialized proteins, transporters, and feedback mechanisms are all part of the intricate systems that control this dynamic process. In this regard, preserving general health requires metal homeostasis [4]. A disturbance in this equilibrium can result in several illnesses, including oxidative stress (caused by excessive metal accumulation), neurodegenerative diseases (caused by copper or zinc imbalance), and anemia (caused by iron imbalance). Thus, knowledge of metal homeostasis is essential for both therapeutic and disease-preventative measures. The control of metal ions, such as iron, zinc, copper, and manganese, which are necessary for many biochemical activities but can be hazardous at high quantities, is known as metal homeostasis in the human body [5]. To preserve healthy physiological processes and avoid toxicity, the body meticulously regulates the absorption, distribution, storage, and excretion of these metals (Fig. **1**) [6].

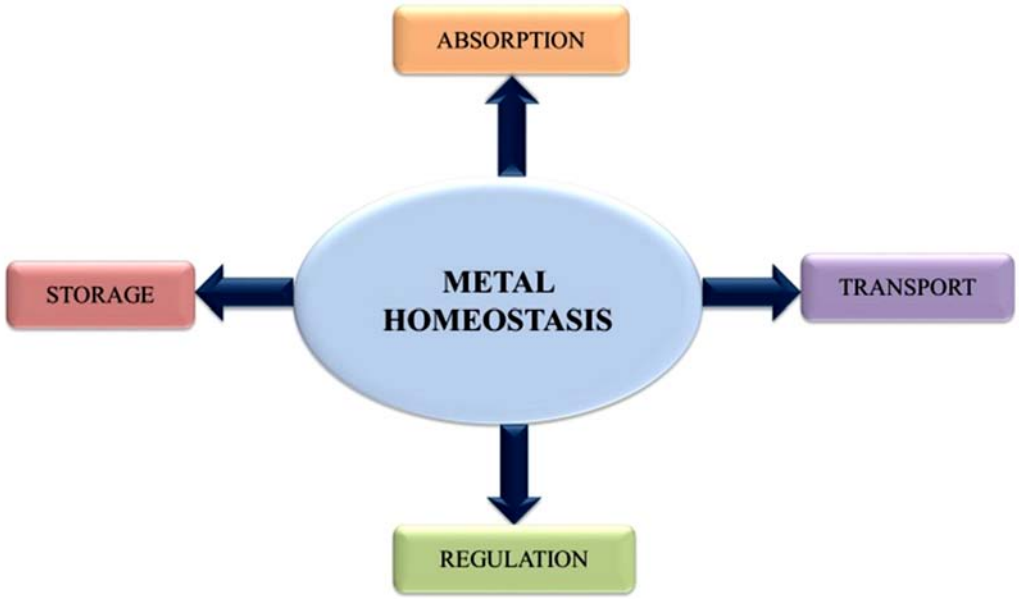

Fig. (1). Breakdown of metal homeostasis.

Significance of Metal Homeostasis and Brain Function

The maintenance of appropriate brain function depends on metal homeostasis. Numerous facets of neuronal activity, such as neurotransmission, synaptic plasticity, and cellular metabolism, depend critically on metal ions like iron, zinc, copper, and calcium. On the other hand, serious neurological problems, such as cognitive impairment, neurodegenerative illnesses, and mental disorders, can result from imbalances in these metals. For this reason, the brain's capacity to control metal ion levels is essential for both normal brain function and general neurological health (Table **1**).

Table 1. Important functions of metals in the brain.

S. No.	Important Functions	Essential Metals	References
1.	Neurotransmission and Synaptic Plasticity	Neurotransmitter release and synaptic signalling depend on zinc and copper. Zinc, for example, regulates synaptic activity and affects the release of neurotransmitters in the synaptic vesicles. Enzymes that control synaptic plasticity, which is essential for memory and learning, depend on copper. Calcium plays a crucial role in activating cellular signaling pathways involved in learning and memory, and it is essential for the release of neurotransmitters during synaptic transmission.	[7, 8]
2.	Enzyme Activity and Energy Metabolism	Several brain enzymes involved in energy production, protein synthesis, and DNA repair depend on metals as essential cofactors. Enzymes involved in mitochondrial activity, for instance, require iron to produce the energy that brain cells need. Copper also contributes to cytochrome c oxidase, a crucial enzyme for mitochondrial respiration.	[9, 10]
3.	Oxidative Stress and Neuroprotection	When there is an imbalance, metal ions, particularly iron and copper, may catalyze the generation of reactive oxygen species (ROS), which can result in oxidative stress. The brain is particularly vulnerable to oxidative damage, which can disrupt neuronal function and exacerbate neurodegenerative conditions like Parkinson's and Alzheimer's.	[11]
4.	Cognitive Function and Neuroplasticity	The brain's capacity for neuroplasticity, the creation of new neural connections, makes zinc especially crucial. Memory problems, learning difficulties, and cognitive deficiencies have all been connected to zinc deficiency. Likewise, iron shortage can affect neurodevelopment and cognitive function, particularly in early life.	[12]

CHAPTER 3

Metal Toxicity and Human Health: Sources, Exposure Routes, and Preventive Strategies

Suraj Sharma[1], Garima Sharma[1], Kousik Maparu[2], Shamsher Singh[2] and **Anil Kumar[1,*]**

[1] *Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, India*

[2] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Environmental pollution from industrial, agricultural, and nutritional sources causes metal poisoning, which is a serious health risk to humans. With an emphasis on their effects on biological systems, this overview examines the several ways that metals may enter the body, such as through the air, water, soil, and food. While hazardous metals like lead, mercury, arsenic, and cadmium disturb cellular homeostasis and result in oxidative stress, neurotoxicity, and organ destruction, essential metals like copper and zinc are essential for physiological processes. Contamination of packaged food and water increases exposure risks and can result in long-term health issues like cancer, heart disease, and developmental abnormalities. Developing preventative measures requires an understanding of the processes behind metal toxicity, such as bioaccumulation, enzyme inhibition, and DNA damage. In order to mitigate metal pollution, this chapter emphasizes the importance of industrial waste management, regulatory frameworks, and bioremediation strategies. To lessen human exposure, better packing materials and environmentally friendly farming methods are also advised. To protect the public from the harmful consequences of metal toxicity, a thorough, interdisciplinary strategy that combines technical innovation, regulatory enforcement, and public awareness is necessary.

Keywords: Cellular homeostasis , DNA damage, Environmental pollution, Metal toxicity, Oxidative stress.

INTRODUCTION

Metals are elements that occur naturally and are essential to biological processes. Certain metals, such as copper (Cu), zinc (Zn), and iron (Fe), are necessary for physiological processes like cellular metabolism, oxygen transport, and enzyme

[*] **Corresponding author Anil Kumar:** Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh, India; E-mail: kumaruips@pu.ac.in

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activity. Traces of these vital metals are necessary to sustain a number of physiological and biochemical processes, but too much of these can be harmful, upsetting cellular balance and resulting in oxidative stress [1]. Conversely, non-essential metals, including arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg), are intrinsically hazardous even at low quantities and have no known biological function. Systemic toxicity may result from the interference of these metals with vital biological functions, such as signaling pathways, DNA repair, and enzyme function. For instance, mercury exposure can result in neurological and renal disorders, while lead exposure has been associated with neurodevelopmental deficiencies, particularly in children [2]. The chemical form, dosage, exposure duration, route of entrance into the body, and a person's genetic and physiological vulnerability are some of the variables that affect how hazardous metals are. Reactive oxygen species (ROS) production, metal homeostasis disruption, inhibition of important metabolic enzymes, and interaction with vital biological components like mitochondria and DNA are just a few of the ways through which metals can cause toxicity [3].

Furthermore, metals can cause chronic health issues by bioaccumulating in organs like the brain, kidneys, and liver. For example, exposure to arsenic is linked to an increased risk of cardiovascular disease and cancer, while cadmium predominantly builds up in the kidneys and causes nephrotoxicity. Toxic metals are a long-term risk to public health because of their persistence in biological and environmental systems [1].

The study of metal toxicity is crucial due to the pervasiveness of metals in the environment, which can be caused by industrial processes, contaminated food and water, or occupational exposure. Gaining an understanding of their toxicological effects aids in the development of focused preventive, early diagnosis, and treatment methods, all of which improve public health outcomes.

EXPOSURE ROUTES OF METALS

The process by which a person is exposed to pollutants that come from a particular source is known as an exposure pathway, according to the Agency for Toxic Substances and Disease Registry [4]. The following five components make up an exposure pathway: the origin of the environmental contamination release; environmental media (including groundwater, surface water, air, soil, sediment, household dust, and biota), which serve to move contaminants from the source to points where human exposure can occur; point of exposure (a location where humans contact a polluted medium, such as a playground, water body, well water, or food services); exposure route (the actual way the contaminant enters or comes into contact with the body, including through ingestion, inhalation, and dermal

absorption); and the receptor population, which consists of those who are exposed to the problematic pollutants at a particular exposure point (Fig. **1**).

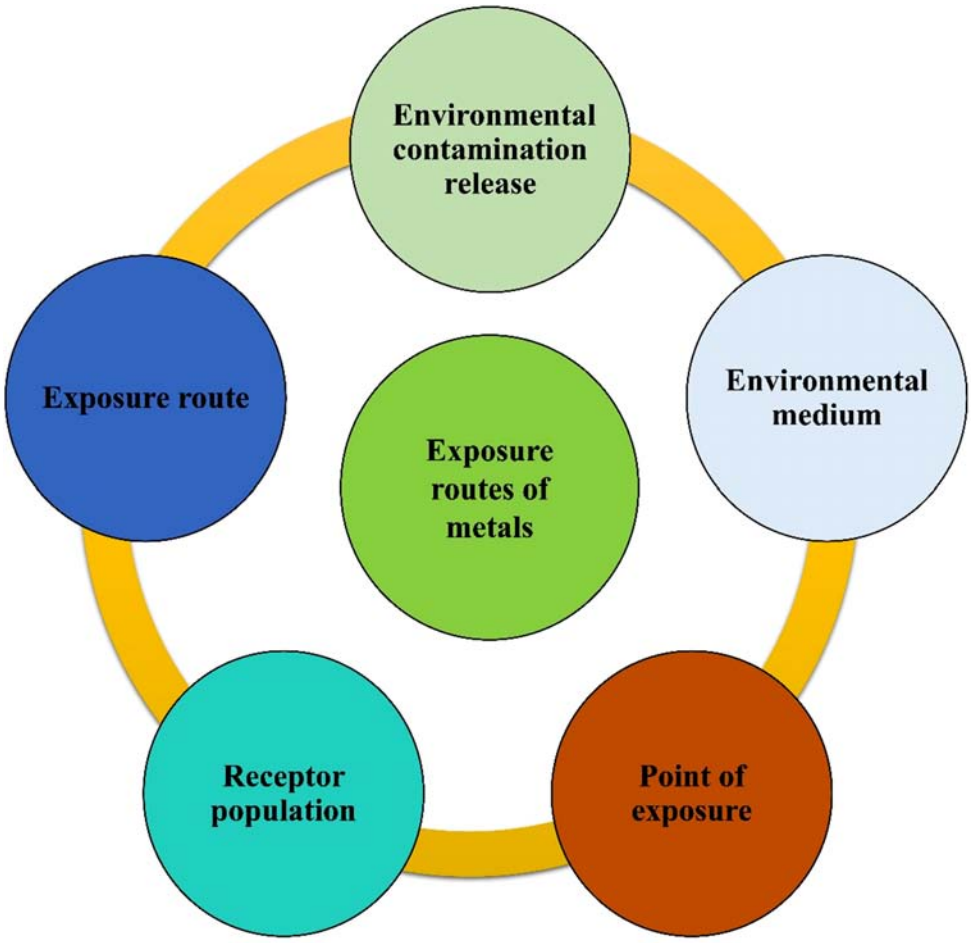

Fig. (1). Exposure routes of metal.

It is important to remember that an exposure pathway is more than just a route of exposure or an environmental medium (such as air, soil, or water). Instead, an exposure pathway consists of every component that connects a receptor population to a source of contamination. However, factors including the degree, frequency, and length of interaction with the contaminated material are essential for measuring exposure. The metal in question also needs to be bioavailable. A biological consequence may develop in the exposed population as a result of the

CHAPTER 4

Epidemiological, Preclinical, and Clinical Status: Targeting Metals' Role and Health Status

Lovekesh Singh[1], Komal[2], G.D Gupta[2], Sanchi Jain[1] and **Shamsher Singh[1,*]**

[1] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

[2] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Healthcare outcomes heavily depend on epidemiological methods because they enable people to understand disease causes and distributions, as well as disease mechanisms. The research conducted in laboratories simultaneously runs clinical trials to study disease patterns and identify risks before confirming the safety and effectiveness of medications. Human health heavily depends on the regulation of essential metals, including iron, zinc, copper, and manganese, because improper levels can lead to serious medical problems. Neuroprotective mechanisms are activated in response to metabolic disturbances, leading to key events that cause cell death. Iron deficiency anemia, hemochromatosis, Wilson's disease, and Menkes disease are all inherited conditions that are exclusively caused by imbalances in body metals. As a result of factors such as genetics, environmental factors, and dietary habits, the prevalence rates of these illnesses vary among metal groups and regions. The severe health challenges caused by heavy metal toxins like lead, mercury, and cadmium affect multiple organs during prenatal growth and infancy because they appear in both industrial areas and natural environments. When coupled with inadequate sanitation and restricted medical access, these health issues are effectively addressed by the combination of drug-resistant parasitic diseases. In laboratories, the integration of mass spectrometry and atomic absorption spectrometry enables health professionals to detect metal imbalances, which in turn empowers physicians to prescribe specific medical treatments. International partnerships are necessary to resolve the security concerns of health security initiatives at the global level, as they are designed to prevent health disparities arising from parasitic infections and metal imbalance.

Keywords: Epidemiology, Global health security, Heavy metals, Iron deficiency anemia, Metal homeostasis, Menkes disease, Neuroinflammation, Neuro-oxidative stress, Wilson's disease.

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; Email: shamshersinghbajwa@gmail.com

INTRODUCTION

Epidemiology is the scientific discipline that investigates the causes, manifestations, and distribution patterns of health conditions and illnesses in particular groups of people [1]. Human data exists in either an epidemiological format, which reveals disease and mortality patterns among exposed populations, or a clinical format, which defines the effects of the substance on individual participants [2]. Healthcare improvement depends significantly on epidemiology, preclinical research, and clinical research. Epidemiology enables crucial public health choices by studying populations through the analysis of diseases and their causes, including exposure risk factors. The evaluation of new treatments through laboratory tests combined with disease mechanism studies is carried out before human trials to validate their effectiveness and safety [3]. Clinical research involves real human subjects to test the safety and effectiveness of treatments, thereby influencing medical treatments and customized patient care. The combined expertise of medical science, preclinical research, and population sciences drives ongoing medical discoveries, leading to improved medical treatment and a reduction in diseases worldwide [4].

COMPREHENSIVE APPROACH TO UNDERSTANDING METAL HOMEOSTASIS AND ITS HEALTH IMPLICATIONS

The term homeostasis refers to stable physical conditions maintained within living systems, while homoeostasis represents this concept in British terminology [5]. The body operates optimally when maintaining specific ranges (homeostatic range) for several variables, including temperature and fluid equilibrium. The management of extracellular fluid pH, sodium, potassium, and calcium ion concentrations, and blood sugar levels remains essential regardless of environmental changes or changes in diet or exercise level [6]. Each of these life-sustaining elements features either one or multiple homeostatic processes or regulators that work together as a unit. All cells maintain their specific metal ion concentrations through the process known as metal homeostasis [7]. A number of biological processes require metal ions as essential components for life maintenance.

Cells utilize transcription factors to control gene expression that oversees metal uptake, storage, and export, which are monitored by combination sensors that include both proteins and riboswitches [8]. Enzymes receive their metal ions through assistance from metallochaperones, while transporters control both cellular entry and exit of these metal ions. The health of our bodies is contingent upon the presence of balanced metal levels, as unregulated metal proportions can result in illnesses that can cause cell death.

Neurotransmission, together with metabolism and central nervous system development, requires essential metal ions, including zinc, copper, magnesium, and manganese, as well as iron, for proper function [9]. Metal homeostasis refers to the processes by which organisms maintain the correct concentrations of essential metal ions in various cellular compartments, which are crucial for life and normal cellular function. An imbalance in metal ions can contribute to the development of neurodegenerative diseases through a variety of mechanisms, including promoting the production and aggregation of pathological proteins, inducing oxidative stress, triggering ferroptosis and cuproptosis, promoting cell senescence, or driving neuroinflammation. Since iron deposits in the brains of patients with PD and AD were first observed in 1924 and 1953, respectively, the relationship between iron dyshomeostasis and neurodegenerative diseases has attracted increasing attention. Abnormal iron deposition in special brain regions has been proven to be positively correlated with disease progression and disease severity in neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Additionally, other metal ions, such as manganese, copper, and zinc, are also found to participate in the development of neurodegenerative diseases by increasing the risk or promoting the aggregation of pathological proteins. Examination of the body's vital metal management to maintain optimal physiology must include exploration of how it controls iron, along with zinc, copper, and manganese. Biological processes depend on these metals because enzyme activity, DNA synthesis, and cellular respiration require them [10]. The body shows multiple health disorders, including anaemia, neurodegenerative conditions, cardiovascular diseases, and immune system breakdown, when metal homeostasis becomes imbalanced through toxicities or inadequate levels. Medical practitioners need to understand how metal-binding proteins interact with transporters to analyze mechanisms of metal transport that lead to disease [11]. The obtained information leads to the development of treatments and screening solutions for diseases of metal origin while revealing their pathophysiological processes.

EPIDEMIOLOGICAL STATUS

Global Trends

Prevalence and incidence of metal imbalance-related diseases: Disease occurrence rates from metal imbalances differ based on which particular metal causes the issue (irrespective of iron, copper, zinc, magnesium, and other metals), as well as the specific diagnosis [12]. Metals are present at abnormal levels in the human body, which disrupts biochemical processes. Excessive or insufficient levels of

CHAPTER 5

Molecular and Cellular Mechanisms of Metal Exposure-related Neurotoxicity

Vaishali Dobhal[1], Falguni Goel[2], Romanpreet Kaur[3] and **Shamsher Singh[3,*]**

[1] *Motherhood University, Roorkee, Uttarakhand, India*

[2] *Department of Pharmaceutical Technology, Meerut Institute of Engineering & Technology (MIET), Meerut, India*

[3] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: A global health risk that affects millions of people globally is environmental exposure to neurotoxic metals and metalloids, including arsenic, cadmium, lead, mercury, and manganese. Environmental metals can alter neurodevelopment, neurobehavior, and cognition, as well as induce neurodegeneration, depending on the lifetime exposure duration. Bioaccumulation of these heavy metals leads to a diversity of harmful effects on a number of bodily tissues and organs. Growth, proliferation, differentiation, damage-repairing mechanisms, and apoptosis are among the biological processes that heavy metals interfere with. A comparison of the mechanisms of action shows that these metals can cause toxicity through comparable pathways, such as the production of ROS, oxidative stress, enzyme inactivation, and weakened antioxidant defence. As the brain consumes a substantial amount of energy, mitochondrial malfunction and the resultant drop in levels of ATP may dramatically affect brain function, resulting in neuronal cell death and associated neurological diseases. Multiple astroglial pathway deficiencies can even cause neurodegeneration. Heavy metal consumption affects the glutamate/GABA-glutamine shuttle, antioxidant machinery, and energy metabolism, among other astroglial homeostatic and neuroprotective cascades. Long-term exposure to heavy metals can cause chronic neuroinflammation, which releases inflammatory mediators and activates immune cells. This can cause damage to neurons, and cognitive impairment leads to neuronal dysfunction. Toxicity analysis of heavy metals can be done by *in vivo* and *in vitro* methods, followed by animal testing and different assays to check the viability of cells, such as MTT, Comet assay, *etc*.

Keywords: Heavy metals, Neurodegeneration, Neuroinflammation, Neurotoxicity, Oxidative stress.

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

INTRODUCTION

Naturally occurring metal elements play vital roles in biological systems. While some basic metals, such as zinc, iron, and copper are essential for regular neurological function, excessive amounts or the introduction of toxic or heavy metals in their different forms, such as lead, mercury, arsenic, and cadmium, can disturb the nervous system's delicate balance, resulting in severe toxicity that compromises a person's natural health [1]. Metals nowadays are used in various fields, especially in industries where they are directly exposed to workers, leading to toxicity and health deterioration. Metal exposures in the workplace and the environment are a result of manufacturing and industrial operations [2]. The production and disposal of hazardous waste, contamination of the air and water, and unintentional spills during the transportation of waste or raw materials are the sources of these exposures. Mineral deposits, volcanic eruptions, and waste discharge are some of the natural sources of metals found in soils and minerals [3]. In order to obtain raw metals for human use, mining and quarrying are essential processes. Metal poisoning has a major effect on brain development, affecting memory, learning, and cognitive processes in both human and animal models. According to clinical research, long-term, excessive metal exposure frequently causes neurological problems such as headaches, dizziness, motor dysfunction, and memory and cognitive deficits. Neurodegenerative processes, which result from a confluence of environmental factors, unhealthy lifestyle choices, and genetic susceptibility, might also be signaled by these symptoms [4]. Patients with Alzheimer's disease (AD) have been found to have higher amounts of heavy metals such as manganese (Mn), mercury (Hg), and cadmium (Cd) in their plasma and cerebrospinal fluid (CSF). In both lab and animal investigations, heavy metals have been found to promote the accumulation of AD-related proteins, such as Tau, ApoE4, and β-amyloid [5]. Furthermore, by hindering the removal of β-amyloid from the brain, these metals worsen its accumulation. With higher iron concentrations seen in the hippocampal and cortical regions of AD patients compared to healthy controls, this research further shows that impaired iron management is an early indicator of AD [6]. A number of enzymes that depend on iron as a cofactor can be inhibited by abnormal iron levels, which can also lead to the creation of β-amyloid and the generation of harmful reactive oxygen species. Although the precise mechanisms are yet unknown, Alzheimer's disease (AD) is commonly associated with several common genetic variants linked to poor iron control. Also, one established risk factor for AD is significant environmental lead (Pb) exposure.

Oral exposure to high levels of lead has been demonstrated in animal experiments to raise levels of pro-inflammatory markers like interleukin-1 (IL-1) and tumor

necrosis factor-alpha (TNF-α), as well as cerebral β-amyloid concentrations. Cognitive impairment is linked to these alterations [7].

Neurotoxicity is defined as damage to the nervous system's structure or function caused by exposure to hazardous substances, especially metals. The category of heavy metals is responsible for serious threats to brain health and development because they can accumulate in neural tissue after passing the blood-brain barrier and lead to various neuropsychiatric disorders like Parkinson's and Alzheimer's disease [8]. In both human and animal models, metal poisoning disrupts brain development and reduces memory, learning, and cognition. Clinically, long-term excessive metal consumption typically causes neurological symptoms such as headaches, dizziness, movement impairments, and memory and cognitive problems [9]. These symptoms can potentially indicate the start of a neurodegenerative process, which is caused by a combination of environmental stressors, unhealthy lifestyle choices, and genetic predispositions. Patients with AD have higher levels of some heavy metals, including Mn, Hg, and Cd, in their plasma and cerebrospinal fluid (CSF). Both *in vitro* and *in vivo*, heavy metals have been shown to enhance the presence of AD-relevant proteins, including Tau, ApoE4, and β-amyloid. Furthermore, by reducing the removal of β-amyloid from the body, heavy metals increase the β-amyloid load [10]. Fig. (**1**) illustrates the fundamental diagram that delineates the heavy metals responsible for neurodegenerative disorders.

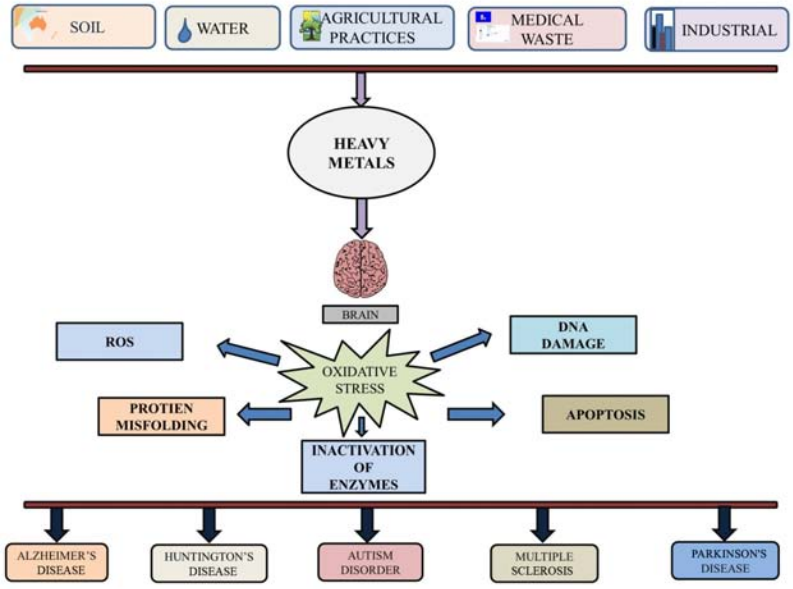

Fig. (1). Basic diagram representing a heavy metal responsible for neurodegenerative disorders.

CHAPTER 6

Metal Exposure and Attention Deficit Disorders: Molecular Mechanisms and Diagnostic Tools

Falguni Goel[1], Vaishali Dobhal[2], Vipin Kumar Garg[1,*], Kousik Maparu[3] and **Shamsher Singh[3]**

[1] *Department of Pharmaceutical Technology, Meerut Institute of Engineering & Technology (MIET), Meerut, India*

[2] *Motherhood University, Roorkee, Uttarakhand, India*

[3] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Attention deficit disorder (ADD) is a neurodevelopmental disorder with a multicausative etiology, such as genetic, environmental, and biological factors, characterized by inattention, impulsivity, and hyperactivity symptoms. Among novel environmental factors, exposure to metals has raised great concern due to their implication in neurotoxicity and mental impairment. Heavy metals such as lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As) are involved in oxidative stress, neuroinflammation, and neurotransmitter dysregulation that play roles in the pathophysiology of ADD. However, the essential metals iron (Fe), zinc (Zn), magnesium (Mg), and copper (Cu) play critical roles in neurodevelopment, and their deficit or imbalance poses a potential risk of exacerbating the symptoms of ADD. The mechanistic processes through which metals impact brain function, including oxidative injury, disruption of dopaminergic and glutamatergic signaling, and epigenetic modifications, are the topic of this chapter. The etiology of metal exposure, ranging from environmental contaminants in air, water, and food to prenatal and neonatal exposure, is debated to highlight key determinants of risk. Furthermore, diagnostic procedures, including biomarker detection and neuroimaging to quantify metal accumulation in ADD subjects, are considered. Interventions such as dietary modification, chelation therapy, and behavioral approaches are also considered, along with future directions in personalized medicine and public health interventions for metal-induced neurotoxicity prevention. Understanding the intricate interaction between metals and ADD can result in targeted therapeutic approaches and policy measures for reducing the risk of environmental exposure.

Keywords: Attention deficit disorder (ADD), Heavy metals, Neurotoxicity, Neurotransmitter dysfunction, Oxidative stress.

[*] **Corresponding author Vipin Kumar Garg:** Department of Pharmaceutical Technology, Meerut Institute of Engineering & Technology (MIET), Meerut, India; E-mail: Vipin.garg@miet.ac.in

Shamsher Singh (Eds.)

INTRODUCTION

ADD is a neurodevelopmental disorder characterized by long-term difficulties with attention, control of impulses, and regulation of cognitive function. ADD occurs among individuals of all ages, and it is commonly evident in childhood, but the issue persists through adulthood. While ADD is typically associated with challenges at school or in the workplace, it also has implications for emotional control, interpersonal relationships, and overall quality of life. The exact etiology of ADD is complex, with an interactive interplay between genetic predisposition, environmental influences, and neurobiological mechanisms [1]. Traditional theories of ADD have focused on deficits in neurotransmitter systems, particularly the dopamine and norepinephrine systems that are essential for attention and executive function. New data suggest that environmental exposures, particularly to metals, contribute importantly to the causation and expression of ADD symptoms [2].

Metals are an integral part of the biological system and participate in various physiological processes such as enzymatic activities, energy metabolism, and neurotransmitter synthesis. Some of the metals, like iron, zinc, and magnesium, play a vital role in proper brain function, involved in synaptic plasticity, neuronal signal transmission, and neuroprotection. But when there is a derangement of such important metals by deficiency or excess, it will cause spectacular neurological disturbances. For instance, altered dopamine signaling, a primary component of ADD pathology, is caused by iron deficiency, and zinc is implicated in the modulation of neurotransmission and synaptic functioning [3]. Magnesium is another critical metal that plays a part in neuronal excitability and synaptic function, and its deficiency has been linked to hyperactivity and mental deterioration [4].

While essential metals have little threat to neurodevelopment and cognitive function, toxic metals like lead, mercury, arsenic, and cadmium are hazardous to neurodevelopment and cognitive well-being. These heavy metals intrude into the body through tainted air, water, diet, and household objects, to which children are especially susceptible because they have developing nervous systems and heightened absorption rates. Exposure to lead, for example, has been explored comprehensively for cognitive dysfunction, behavioral dysfunctions, and a decrease in the span of attention [5]. Even in moderate exposure, lead interferes with the functioning of synapses, decreases the transmission of signals from calcium ions, and initiates oxidative damage to the brain tissue. These effects form part of ADD neurological deficiencies. Mercury, a second neurotoxic metal, also builds up in the brain and impacts neurotransmitter activity, resulting in delays in cognitive development and attentional issues. Exposure to arsenic has

been associated with neuroinflammation, which enhances symptoms of ADD by affecting cognitive processing and executive function. Cadmium also interferes with dopaminergic circuitry, again contributing to attention deficit and behavioral abnormalities [6].

The involvement of metals in neurological conditions, such as ADD, has emerged as an important area of research because of their ability to modify neurodevelopmental pathways. Heavy metals are known to induce oxidative stress, promote neuroinflammation, and disrupt synaptic connectivity, leading to long-term cognitive as well as behavioral dysfunctions. On the other hand, deficiencies in essential metals impair neuronal function, compromising the brain's ability to maintain attention and regulate cognitive functions effectively. It is highly essential for establishing targeted therapeutic approaches and preventive treatments to understand the complicated interassociation of metal exposure, neurodevelopment, and ADD [7]. By discovering metal imbalance detection and minimizing the exposure to surroundings, scientists and healthcare professionals can find new opportunities in treating as well as curbing the influence of ADD. The new field of research focuses on the need for an all-embracing approach considering both environmental and nutritional factors in comprehending attention disorders [8].

METALS AND BRAIN FUNCTION

Metals are of prime significance to brain physiology, impacting a variety of neurological processes such as neurotransmitter regulation, synaptic plasticity, and oxidative balance. While some metals are critical to neurodevelopment and cognition, others can be highly detrimental due to their neurotoxicity. A delicate homeostasis balance of metals is crucial to maintain optimal brain condition, and every disturbance, whether caused by deficits in required metals or by intense exposure to poisonous metals, results in neurodevelopmental disorders, such as ADD [9].

Essential metals like iron, zinc, magnesium, and copper have been implicated in the maintenance of the fundamental neurological processes. Iron is essential for myelination and dopamine metabolism, both of which are critical in executive function and attention control. Zinc affects synaptic transmission and neuronal communication, while magnesium regulates neurotransmitter release and protects against excitotoxicity [10]. Copper is involved in enzymatic processes that assist in maintaining energy metabolism and antioxidant defense in the brain. Deficiency of one of these metals leads to mental deficits, learning difficulties, and behavior disorders common in ADD.

CHAPTER 7

Aluminium Exposure Routes, Absorption, and Excretion Mechanism

Sania Grover[1], R.K. Narang[2], G.D. Gupta[2], Kousik Maparu[1] and **Shamsher Singh[1,*]**

[1] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

[2] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Aluminium is an extensively dispersed environmental metal with important implications for human health. The exposure to aluminium is *via* various routes, viz., ingestion from contaminated food, water, and drugs, inhalation in occupational and environmental contexts, and skin contact. Prenatal exposure also evokes concern about developmental toxicity. The uptake of aluminium is mainly *via* the gastrointestinal tract, respiratory system, and skin, with systemic bioavailability being a function of chemical speciation and physiological considerations. The excretion routes are urinary and fecal elimination, with minor contributions from sweat and skin desquamation. Aluminium is increasingly involved in the pathogenesis of numerous neurological disorders. Its neurotoxicity is linked to oxidative stress, neuroinflammation, mitochondrial dysfunction, and metal homeostasis disruption, leading to the development and progression of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Huntington's disease. Aluminium toxicity detection requires sophisticated analytical methods, including neuroimaging techniques. Strategies in mitigation include both pharmacological measures, *i.e.*, chelating compounds and antioxidants, and non-pharmacological measures, *i.e.*, dietary changes and environmental control. Future studies need to identify new biomarkers of aluminium neurotoxicity and refine more sensitive neuroimaging modalities to monitor aluminium deposition in the brain. Knowledge of the long-term effects of aluminium exposure is important for developing preventive and therapeutic interventions. With its prevalence and possible neurotoxicity, ongoing research on aluminium toxicology is still important for public health and regulatory issues.

Keywords: Aluminium, Alzheimer’s disease, Amyotrophic lateral sclerosis, Huntington's disease, Multiple sclerosis, Parkinson’s disease.

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

Shamsher Singh (Eds.)

INTRODUCTION

Aluminium (Al) is the third most abundant element that exists in the earth's crust, but the most predominantly distributed metal within the earth, though it shows no known roles in human life [1]. Al, a ubiquitous environmental metal, enters the human body through multiple exposure routes, including ingestion (contaminated food and water), inhalation (industrial emissions, dust), and dermal contact (cosmetics, pharmaceuticals). Excess exposure to such Al has attracted attention to its toxic consequences, especially on nervous tissues, kidneys, and bones [2]. Once absorbed, primarily in the gastrointestinal tract (with low bioavailability) or lungs, it binds to transferrin and albumin, facilitating systemic distribution, particularly to the brain and bones. The kidneys serve as the primary excretory route, efficiently clearing aluminum in healthy individuals, while impaired renal function can lead to bioaccumulation and toxicity. Toxicology deals with such an understanding of the absorption, metabolism, accumulation, and mechanisms of toxic activity on biological processes [3]. While Al naturally occurs in the environment, most human exposure is through anthropogenic activities, including industrial processes, pharmaceutical use, and dietary sources. Chronic exposure to Al has been linked to neurotoxicity, oxidative stress, and diseases like Alzheimer's and osteomalacia [4]. Understanding aluminum's pharmacokinetics is crucial in assessing its long-term implications for neurotoxicity, oxidative stress, and metabolic disorders.

SOURCES OF ALUMINIUM EXPOSURE

Al occurs in natural and anthropogenic sources [5]. Knowledge of sources is essential in estimating exposure risk and regulation.

Natural Sources

Soil and Rocks: Al is naturally found in rocks, clay, and minerals like bauxite. Water Bodies: Groundwater and surface water can contain Al due to leaching by adjacent rocks. Volcanic Activity: Natural volcanic activity releases Al into the atmosphere.

Anthropogenic Sources

Food and Beverages: Al is used widely as a food additive (E173) in baked food items, anticaking products, and processed cheese. Food packages, utensils, and cans containing Al lead to the leaching of Al into food.

Pharmaceuticals and Personal Care Products

Antacids and Vaccines: Al hydroxide finds widespread application in antacids and as a vaccine adjuvant. Deodorants and Cosmetics: Al chlorohydrate finds common use as a frequent ingredient in cosmetics and antiperspirants, leading to dermal exposure.

Industrial Emissions

Al smelting, refining, and recycling processes emit large amounts of Al dust and fumes into the atmosphere. Welding and grinding procedures during production are occupational exposure sources.

Water Treatment

Al sulfate (alum) is employed in water treatment facilities as a coagulant to clear impurities. Residual Al in treated water accounts for the daily intake.

GLOBAL BURDEN OF ALUMINIUM EXPOSURE

Worldwide Al exposure varies depending on environmental factors, industrial practices, and eating habits [6]. High rates of Al contamination have been reported across various regions of the world, and this causes health issues in the population.

Aluminium Contamination in Drinking Water

Government bodies, such as the World Health Organization (WHO) and the Environmental Protection Agency (EPA), have provided guidelines for Al contamination in drinking water. In some countries, drinking water Al content surpasses acceptable standards, increasing exposure risks [7].

Trends in Occupational Exposure

Heightened Al manufacturing and mining processes in some areas report enhanced occupational exposure. Countries such as China, India, the United States, and Russia have widespread Al industries, putting workers at risk of respiratory and neurological disorders [6].

Dietary Exposure

According to studies, Al exposure *via* food is reliant on geographical dietary habits. Acidic beverages and processed foods containing Al packaging contribute to the rising exposure levels in urban populations [8].

CHAPTER 8

Possible Toxicity of Lead and its Role in the Progression of Neurodegenerative Disorders

Navpreet Kaur[1], Yukti Mittal[1], Ramandeep Kaur[1], Shamsher Singh[2,*] and **Khadga Raj Aran[2,*]**

[1] *Department of Pharmacy Practice, ISF College of Pharmacy, Moga, Punjab, India*

[2] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Lead (Pb) is a neurotoxic heavy metal that poses several risks to human neurological health through exposure for a long period at low concentrations. Its ability to cross the blood-brain barrier (BBB) facilitates lead-induced neurodegeneration via several mechanisms, such as amyloid-β (Aβ) plaque deposition, tau hyperphosphorylation, degeneration of dopaminergic neurons, and loss of synaptic plasticity. They result from interconnected processes: oxidative stress, mitochondrial dysfunction, disruption of calcium signaling, and epigenetic dysregulation. These processes drive neurodegeneration in Alzheimer's disease (AD) through Aβ/NFT deposition, Parkinson's disease (PD) through α-synuclein aggregation and dopamine loss, multiple sclerosis through immune dysregulation and BBB disruption, and Amyotrophic Lateral Sclerosis (ALS) through motor neuron apoptosis. Furthermore, lead exposure exacerbates this condition by disrupting copper homeostasis, microRNA networks, and glial activation, worsening neuroinflammation and protein misfolding. Therefore, different detection strategies, such as blood lead level (BLL) screening, X-ray fluorescence (XRF) for bone lead measurement, and inductively coupled plasma mass spectrometry (ICP-MS) for trace analysis of Pb, are essential for early intervention and prevention of its accumulation. This book chapter discusses the detailed mechanisms of lead-induced toxicity, along with different detection techniques to detect lead-induced neurological damage, which provides vital information to reduce its burden in neurodegenerative disorders.

Keywords: Calcium dysregulation, Lead, Neurodegenerative diseases, Oxidative stress, Synaptic dysfunction.

[*] **Corresponding author Shamsher Singh and Khadga Raj Aran:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India, E-mail: bishalarann@gmail.com, shamshersinghbajwa@gmail.com

Shamsher Singh (Eds.)

INTRODUCTION

Lead (Pb) is a neurotoxic heavy metal that poses several risks to human neurological health through exposure for a long period at low concentrations. Its ability to cross the blood-brain barrier (BBB) facilitates lead-induced neurodegeneration via several mechanisms.

ROLE OF LEAD IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a chronic neurological disorder that accounts for at least two-thirds of dementia cases among older adults and is characterized by a gradual loss of cognitive function and behavioural abilities, including memory, understanding, language, attention, reasoning, and judgement. The key AD pathological characteristics consist of the amyloidogenic processing of the amyloid precursor protein (APP), the deposition of extracellular amyloid beta (Aβ), hyperphosphorylation of tau, and synthesis of neurofibrillary tangles (NFTs) in nerve cells [1]. Chronic heavy metal exposure, including aluminium, cadmium, mercury, and lead (Pb), increases the production of inflammatory cytokines, which promotes neuroinflammation and neuronal loss [2]. Pb is a toxic heavy metal, which is involved in numerous pathophysiological mechanisms that contribute to the underlying AD pathophysiological processes, such as mitochondrial dysfunction, copper dysregulation, neuroinflammation, and miRNA-mediated gene regulation. Chronic Pb exposure activates NFκB, which is a key regulator of neuroinflammation, along with increasing the expression of β-secretase (BACE1), involved in amyloidogenic processing of Aβ and production of Aβ aggregates [3]. Additionally, this NFκB activation increases the expression of glycogen synthase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5), which results in hyperphosphorylation of tau at multiple sites and formation of NFTs (Fig. **1**) [4, 5]. Moreover, the activation of NFκB increases the expression of NLRP3 and caspase 1, as well as the production of IL1β and IL-18, resulting in blood-brain barrier (BBB) disruption, neuronal injury, and synaptic dysfunction [6]. Additionally, Pb exposure can trigger microglial activation by increasing intracellular copper concentrations, which enhance the release of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), resulting in neuroinflammation and neuronal damage. In addition, Pb can upregulate the expression of copper transporter 1 (CTR1) and downregulate copper P-type ATPase transporter (ATP7A) in the hippocampal neurons and microglia, resulting in disruption of copper homeostasis. Disruption of this homeostasis further contributes to increased copper accumulation in mitochondria through copper transporter COX17, resulting in increased production of mitochondrial reactive oxygen species (mtROS), impaired electron transport

chain, and oxidative stress. Moreover, Pb exacerbates this condition by increasing the mitochondrial import pathway of apoptosis-inducing factor (AIF) and coiled-coil-helix-coiled-coil-helix domain containing protein 4 (CHCHD4), which results in increased oxidative stress, mitochondrial homeostasis disruption, impaired protein folding, and apoptosis. This mitochondrial dysfunction further contributes to neuronal apoptosis and synaptic dysfunction, and finally, AD pathology [7]. Furthermore, Pb enters neurons through voltage-gated calcium channels, disrupting calcium signaling by competing with calcium (Ca^{2+}) and exacerbating synaptic dysfunction, mitochondrial dysfunction, and inflammatory response. Moreover, Pb inhibits N-methyl-D-aspartate (NMDA) receptors and reduces Ca^{2+} influx, which further impairs long-term potentiation, a key mechanism involved in learning and memory [8]. Pb furthermore exacerbates synaptic dysfunction and cognitive deficits by mimicking Ca^{2+} and binding with calmodulin and protein kinase C (PKC), resulting in their dysfunction and aberrant activation of intracellular signaling pathways [9].

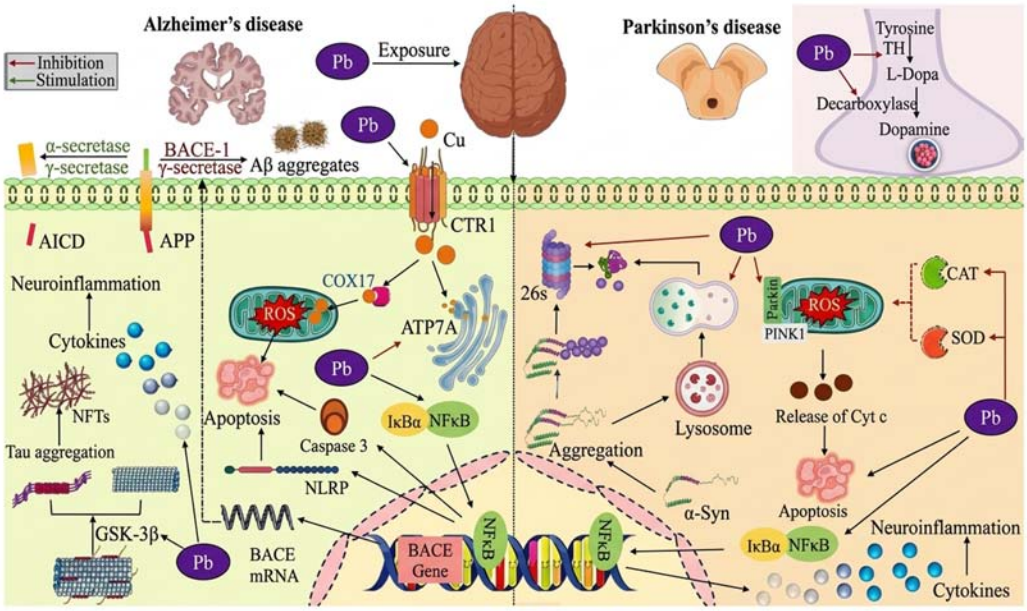

Fig. (1). Lead exposure regulates cell pathways in Alzheimer's disease (AD), disrupts copper homeostasis, increases expression of NLRP, BACE1, GSK-3β, and caspase 3 via NFκB signaling pathway (On the left side). In Parkinson's disease (PD), it inhibits the synthesis of dopamine via inhibiting TH and decarboxylase, as well as preventing degradation of α-Syn by inhibiting its proteasomal degradation (On the right side). Furthermore, it results in mitochondrial dysfunction by hyper-methylating PINK1 and PARK, promoting apoptosis and inhibiting the activity of antioxidant enzymes, along with promoting neuroinflammation via the NFκB pathway.

CHAPTER 9

Physiological and Pathological Role of Iron in Neurological Disorders

Lav Goyal[1], R.K. Narang[2], Dhrita Chatterjee[1], Kousik Maparu[1] and **Shamsher Singh[1,*]**

[1] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

[2] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Iron is a crucial nutrient essential for the optimal functioning of the central nervous system (CNS). It plays a vital role in oxygen transport, energy metabolism, and neurotransmitter synthesis. An imbalance in iron levels, whether deficiency or excess, can disrupt iron homeostasis, leading to oxidative stress, inflammation, and protein aggregation. Such disruptions are linked to several neurological disorders, including Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS). Excess iron accumulation can interfere with the Fenton reaction, generating oxidative stress and contributing to mitochondrial dysfunction. In Parkinson's disease, iron deposits contribute to the formation of Lewy bodies, a key pathological feature of the condition. Additionally, iron overload is associated with tau hyperphosphorylation, leading to neurofibrillary tangles commonly found in Alzheimer's disease. Moreover, excessive iron levels contribute to demyelination and motor neuron degeneration, accelerating the progression of neurodegenerative disorders. Advancements in medical technology have enhanced the ability to detect iron accumulation in the brain. Diagnostic techniques include X-ray imaging, MRI-based methods, transcranial sonography, and cerebrospinal fluid analysis. Several iron-chelating agents, such as deferoxamine, deferasirox, and deferiprone, are available for therapeutic use to counteract iron toxicity. A deeper understanding of iron's involvement in neurodegeneration can lead to developing novel therapeutic strategies to slow or prevent disease progression. This chapter explores the role of iron in CNS function, the consequences of iron dysregulation, available detection methods, and potential treatment approaches for iron-related neurodegenerative disorders.

Keywords: Iron, Iron homeostasis, Iron chelators, Iron detection techniques, Neurological disorders.

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

INTRODUCTION

Iron is a vital trace element in numerous physiological processes, including oxygen transport, energy metabolism, and neurotransmitter synthesis. It plays a crucial role in brain function, but dysregulation of iron levels can contribute to various neurological disorders [1]. Maintaining iron homeostasis is essential, as deficiency and overload can lead to neural dysfunction and neurodegeneration. Iron homeostasis is the precise regulation of iron uptake, storage, and utilization, ensuring optimal cellular function. The brain has a unique iron regulatory system, which includes transport proteins such as transferrin, ferroportin, and ferritin [2]. Disruptions in these mechanisms can result in iron accumulation, a common pathological feature of neurodegenerative diseases. Emerging research highlights iron's role in several neurodegenerative conditions, including Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [3].

In Parkinson's disease, degeneration of dopaminergic neurons in the substantia nigra is a hallmark feature, with studies showing significant iron accumulation in this region. Excess iron contributes to oxidative stress, mitochondrial dysfunction, and impaired dopamine metabolism [4]. It also interacts with α-synuclein, promoting its aggregation into Lewy bodies, a key pathological characteristic of PD [5]. Furthermore, iron-induced neuroinflammation exacerbates neuronal damage, making it a crucial factor in disease progression [6]. Alzheimer's disease, the most prevalent form of dementia, is marked by amyloid-beta plaques and neurofibrillary tangles [7]. Iron dysregulation plays a significant role in AD by accelerating amyloid-beta aggregation and increasing oxidative stress, contributing to neuronal damage and cognitive decline [8]. Elevated iron levels in specific brain regions strongly correlate with worsening neuroinflammation and disease progression. Understanding iron's involvement in AD pathology can pave the way for novel therapeutic interventions [9]. In multiple sclerosis, a chronic autoimmune disorder affecting the central nervous system, iron accumulation in microglia and oligodendrocytes intensifies inflammatory responses, oxidative stress, and myelin degradation [10, 11]. Disruptions in iron metabolism may worsen disease severity, making it a potential target for therapeutic strategies [12]. Similarly, in ALS, excessive iron accumulation in the motor cortex and spinal cord has been linked to oxidative stress, mitochondrial dysfunction, and motor neuron degeneration. Iron-dependent enzymes play a role in disease progression, highlighting the potential for iron-modulating therapies in ALS treatment [13, 14].

Excess iron contributes to oxidative stress, inflammation, and protein aggregation, ultimately accelerating neurodegeneration. As a result, iron chelation therapy and advanced iron detection techniques have gained attention in both research and

clinical settings. Iron chelators such as deferoxamine, deferasirox, and deferiprone have been explored for their potential to mitigate iron-related toxicity in neurodegenerative diseases [15]. These chelators can cross the blood-brain barrier, regulate iron levels, and reduce their harmful effects [16]. Accurate brain iron accumulation detection is critical for understanding its role in neurodegeneration and evaluating treatment efficacy. Advanced imaging techniques provide valuable insights into iron distribution and accumulation patterns, including MRI-based quantitative susceptibility mapping (QSM), X-ray fluorescence (XRF), transcranial sonography, and cerebrospinal fluid analysis. These methods enable early diagnosis and monitoring of disease progression, supporting the development of targeted therapeutic approaches [17].

IRON HOMEOSTASIS

Iron homeostasis is a tightly regulated process that ensures optimal iron levels to support physiological functions while preventing toxicity. The body controls iron absorption, transport, and storage to meet metabolic demands and avoid imbalances [18]. The liver is the primary storage site, where iron is bound to ferritin, while transferrin transports it into the bloodstream to meet cellular needs [19]. Ferroportin, the only known iron exporter, plays a critical role in systemic iron regulation by controlling iron release into circulation. Due to its high metabolic activity, the brain requires substantial iron levels [20]. Neurons, oligodendrocytes, and microglia rely on iron for essential processes such as myelination, neurotransmission, and mitochondrial respiration [21]. However, the blood-brain barrier (BBB) challenges iron transport, necessitating specialized mechanisms for efficient uptake and distribution within the central nervous system [22].

Oxygen Transport

One of iron's primary roles is in oxygen transport, a fundamental process for sustaining life. Haemoglobin, a protein found in red blood cells, contains iron in its heme groups, enabling efficient oxygen transport from the lungs to tissues throughout the body [23]. Similarly, myoglobin in muscle cells utilizes iron to store and release oxygen during muscle contraction and metabolic processes [24]. An adequate oxygen supply in the brain is vital for neuronal survival and function. Iron deficiency can lead to anaemia and hypoxia, reducing oxygen availability for cerebral cells, which may impair cognitive function, memory retention, and neural plasticity [25, 26]. Chronic hypoxia has been linked to neurodegenerative diseases, as it exacerbates oxidative stress and neuronal damage [27]. Iron-dependent enzymes, such as prolyl hydroxylases, regulate hypoxia-inducible factors (HIFs), influencing gene expression in response to

CHAPTER 10

Genetic Variation and Mutation in Neurodegenerative Disorders: Impact of Various Genes

Kamal Preet Mehra[1], Nileshwar Kalia[2] and **Shamsher Singh[2,*]**

[1] *Department of Pharmacology, RIMT University, Sirhind, Mandi Gobindgarh, Punjab, India*

[2] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: This chapter explores the intricate role of genetic variations and oxidative stress pathways in the etiology and progression of neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD). It highlights how genetic mutations in key genes like APP, PSEN1, PSEN2, SNCA, LRRK2, PRKN, and PINK1 are linked to familial forms of these disorders, while environmental and epigenetic factors also contribute significantly. Metal-induced neurotoxicity in brain regions such as the hippocampus and basal ganglia, triggered by elements like lead, manganese, and iron, is discussed in depth. The chapter emphasizes the impact of metal transport genes (HFE, SLC40A1, and ATP13A2) and detoxification enzymes such as glutathione S-transferases (GSTs) and metallothioneins (MTs) in mitigating oxidative damage. Special focus is given to antioxidant defense pathways involving superoxide dismutase (SOD) and catalase (CAT), detailing their biochemical mechanisms and regulatory functions. Dysfunction in these enzymes due to genetic mutations, oxidative overload, or aging correlates strongly with increased vulnerability to neuronal damage and disease progression. By integrating molecular genetics, toxicology, and enzymology, the chapter underscores the significance of maintaining redox homeostasis and suggests therapeutic potential in targeting antioxidant pathways for managing neurodegenerative conditions.

Keywords: Antioxidant enzymes, Genetic mutation, Metal toxicity, Neurodegeneration, Oxidative stress.

INTRODUCTION

Neurological disorders encompass a wide range of conditions that affect the nervous system, including the brain, spinal cord, and peripheral nerves. These

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

disorders can manifest in various forms, such as cognitive impairments, motor dysfunctions, sensory deficits, and emotional disturbances. Common neurological disorders include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), epilepsy, and multiple sclerosis (MS). The etiology of these disorders is often complex, involving a combination of genetic, environmental, and lifestyle factors. Genetics plays a crucial role in the development and progression of many neurological disorders. Advances in genetic research have identified numerous genes and genetic mutations associated with these conditions. For instance, mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes are linked to familial forms of AD. Similarly, mutations in the leucine-rich repeat kinase 2 (LRRK2) and alpha-synuclein (SNCA) genes are associated with familial PD.

In ALS, mutations in the superoxide dismutase 1 (SOD1) gene and the C9orf72 gene are known to contribute to the disease. Genetic predisposition can influence the susceptibility to neurological disorders, the age of onset, and the severity of symptoms. However, the presence of a genetic mutation does not always guarantee the development of a disorder, as environmental factors and gene-environment interactions also play significant roles. For example, exposure to toxins, infections, and lifestyle factors such as diet and physical activity can modulate the risk and progression of these conditions. Understanding the genetic basis of neurological disorders has significant implications for diagnosis, treatment, and prevention. Genetic testing can help identify individuals at risk, enabling early intervention and personalized treatment strategies. Moreover, research into the molecular mechanisms underlying these genetic mutations can lead to the development of targeted therapies aimed at correcting or mitigating the effects of these mutations. As our knowledge of genetics and its role in neurological disorders continues to expand, it holds promise for improving the lives of those affected by these debilitating conditions.

SUSCEPTIBILITY OF METAL-INDUCED NEUROTOXICITY (HIPPOCAMPUS/ BASAL GANGLIA)

Susceptibility of the Hippocampus to Metal-induced Neurotoxicity

The hippocampus is a critical brain region involved in memory formation, learning, and spatial navigation. It is highly susceptible to metal-induced neurotoxicity due to its high metabolic activity and the presence of numerous synaptic connections.

Lead (Pb)

Lead exposure is particularly harmful to the hippocampus. It can result in oxidative stress, mitochondrial dysfunction, and disruption of calcium homeostasis. Lead exposure in children has been linked to decreased intellectual ability, impaired verbal concept formation, difficulty with grammatical reasoning, and poor command following. In adults, occupational exposure to lead has shown impairment of verbal and visual memory performance, lower decision-making speed, and deficits in visuomotor coordination.

Zinc (Zn)

Zinc is essential for normal brain function, but both deficiency and excess can be harmful. Excessive zinc can suppress copper and iron absorption, promote reactive oxygen species (ROS) production, disrupt metabolic enzyme activities, and activate apoptotic processes. Disruption of zinc homeostasis has been associated with Alzheimer's disease (AD), brain trauma, cerebral ischemia, epilepsy, and vascular-type dementia. High levels of zinc can enhance the formation of fibrillar β-amyloid aggregation, leading to neurodegeneration.

Susceptibility of the Basal Ganglia to Metal-induced Neurotoxicity

The basal ganglia are a group of nuclei in the brain involved in motor control, coordination, and various cognitive functions. They are particularly vulnerable to metal-induced neurotoxicity due to their role in dopamine regulation and high iron content.

Manganese (Mn)

Manganese is essential for various biological processes, but overexposure can lead to neurotoxicity. Chronic manganese exposure can cause manganism, a condition characterized by tremors, lethargy, speech impediments, and psychosis. Manganese accumulates in dopaminergic neurons of the substantia nigra, a part of the basal ganglia, leading to motor deficits similar to those observed in Parkinson's disease (PD). Elevated manganese levels can increase ROS production, mitochondrial dysfunction, and autophagy dysregulation, contributing to neuronal death.

Iron (Fe)

Iron is crucial for oxygen transport and various redox reactions. However, excessive iron accumulation in the brain can lead to increased ROS levels, lipid peroxidation, protein oxidation, DNA damage, and mitochondrial fragmentation. Iron dyshomeostasis has been linked to several neurological disorders, including

CHAPTER 11

Diagnostic and Therapeutic Approaches to Neurodegenerative Disorders: Biomarkers for Early Detection

S.K. Abdul Rahaman[1,*], Sakshi Patel[1], Sanchi Jain[3], Prem Shankar Mishra[1], Rahul Kumar[1], Naga Rani Kagithala[1], Ajay Bommareddy[2] and **Shamsher Singh[3]**

[1] *School of Medical & Allied Sciences, Department of Pharmacy, Galgotias University, Greater Noida, Uttar Pradesh, India*

[2] *Biomedical Science Department, Schmidt College of Medicine, Florida Atlantic University, Boca Raton, Florida, USA*

[3] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Early detection of metal-induced neurotoxicity is critical for preventing and managing neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's disease. These sections highlight the growing importance of diagnostic and therapeutic strategies centred on metal-related biomarkers. Advances in molecular biology and neuroimaging have enabled the identification of specific biomarkers, such as metal-binding proteins, metalloproteins, and oxidative stress indicators, that reflect the early pathological changes. These biomarkers offer promising tools for non-invasive diagnosis, disease staging, and therapeutic monitoring. Emerging imaging modalities and biosensor technologies further enhance the ability to track metal accumulation and distribution in real time. On the therapeutic front, strategies targeting metal dysregulation, such as chelation therapy, metal transporter modulators, and nanocarrier-based drug delivery, are under active investigation. Personalized medicine approaches guided by biomarker profiles are paving the way for tailored inventions. These integrated approaches focus on yearly biomarker-targeted therapy and represent a transformative shift in managing metal-associated neurological disorders with precision and efficacy.

Keywords: Biomarkers, Bioluminescent sensors, Chelating agents, Electrochemical sensors, Inductively coupled plasma mass spectrometry.

[*] **Corresponding author S.K. Abdul Rahaman:** School of Medical & Allied Sciences, Department of Pharmacy, Galgotias University, Greater Noida, Uttar Pradesh, India; E-mail: rahamandr123@gmail.com

Shamsher Singh (Eds.)

INTRODUCTION

Neurological disorders present as an extensive group of diseases affecting the brain, spinal cord, and the peripheral nervous system [1]. These medical disorders display neural process dysfunctions that result in cognitive, motor, and behavioural impairments [2]. The continuous rise in global neurological disease prevalence leads to Alzheimer's disease among millions of people, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS) among millions of people [3]. Research shows that toxic metals are major contributors to disease development and disease progression in neurological disorders, even though experts usually link neurological decline to aging factors, genetic risks, and environmental conditions. Studies link metals to neurological dysfunction, although new research points to metals as fundamental factors leading to multiple neurological disease pathologies [4]. Scientific studies recognize lead, mercury, arsenic, cadmium, and aluminium as posing dangerous health risks to humans [5]. These harmful substances affect important biological mechanisms, which results in cell damage, brain inflammation, and death of nerve cells. Metals cause neurotoxicity through their capacity to disrupt brain cellular homeostasis while simultaneously creating disruptions in neurotransmitter activity [6].

Metals drive neurological damage as an initial mechanism by triggering oxidative stress formation [7]. Many toxic metals drive cellular ROS generation, exceeding natural antioxidant defences, thus causing cellular destruction. Oxidative stress attacks neuronal membrane proteins and DNA, triggering a series of interconnected reactions that end in neuronal destruction or death. The harmful effects of stress-induced oxidation significantly amplify neuroinflammatory responses present in numerous neurodegenerative diseases, including Alzheimer's and Parkinson's disease [8]. Metals disrupt fundamental cellular processes that sustain neural function during their interactions with brain tissue. Numerous papers demonstrate how lead and mercury cause disruption of neural calcium homeostasis, which generates excitotoxic damage and results in cellular loss [9]. Metals disrupt mitochondrial function, which reduces cellular energy production while simultaneously making neurons more susceptible to injury [10].

Brain neurotransmitter systems interact with metals in ways that create additional neurological damage. Three essential brain neurotransmitters, dopamine, serotonin, and glutamate, control mood networks and motor functions together with cognitive processes [11]. Neurotransmitter release, receptor binding, and signal transduction pathways exhibit interference from metal substances, including mercury, lead, and manganese. Disabilities caused by these disruptions result in different neurological conditions, including cognitive deficits, motor dysfunction, and mood disturbances [12]. The investigation into neurologic

disorders caused by metals faces additional challenges because these toxic substances remain in environmental elements and build up during body retention. Long-term small doses of toxic metals frequently produce chronic health problems that emerge multiple years after initial exposure, making it hard to detect a clear cause-and-effect relationship [13]. Research shows that children develop developmental delays and cognitive impairments because of lead exposure through contaminated water and paint, and adults develop neurodegenerative diseases from this toxicant [14]. Exposure to mercury specifically through environmental pollution, together with contaminated seafood consumption, has been scientifically linked to diverse neurological symptoms ranging from rapid movements to impaired memory and cognitive brain function problems [15].

Research shows that metal exposure leads to complex neurological disorders that combine multiple influencing variables. The main mechanisms of neurological injury when metals attack nervous tissue are oxidative stress, excitotoxicity, and disruption of chemical messaging [16]. The understanding of the mechanisms by which metals generate neurotoxic outcomes remains essential to developing both detection methods and therapeutic solutions for future environmental exposure risks [17]. Detecting biomarkers for both toxicant exposure and toxic levels will help doctors diagnose neurological diseases before they become severe so that they can cut down the destructive impact of harmful substances [18].

FUNDAMENTALS OF METAL BIOMARKERS AND THEIR CONNECTION TO NEUROLOGICAL CONDITIONS, INCLUDING DETECTION TECHNIQUES

The identification of metal biomarkers represents a critical step essential for both early detection and diagnosis, along with monitoring neurological disorders related to metal toxicity [19]. Shared preferences plausibly identify toxic metals that show neurotoxicity through their destructive power against biological operations within the nervous system [20]. Increased global industrialization has produced a more widespread distribution of toxic metals, which now requires heightened attention regarding their involvement in neurological disease development.

Neurotoxicant metals, including lead, mercury, arsenic, and aluminium, together with cadmium, remain principal environmental contributors to chronic neurological conditions, including Parkinson's and Alzheimer's disease, along with multiple sclerosis [21]. Children exposed to lead during early development experience cognitive disabilities and developmental setbacks, resulting in behavioral problems [22]. Additionally, mercury causes neural damage that leads

CHAPTER 12

Metal Dysregulation in Neurodegenerative Disorders: Mechanistic, Preclinical, and Clinical Aspects

Lovekesh Singh[1], G.D. Gupta[2], Romanpreet Kaur[1] and **Shamsher Singh[1,*]**

[1] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

[2] *Department of Pharmaceutics, ISF College of Pharmacy (An Autonomous College), Moga, 142001, Punjab, India*

Abstract: Major health issues like cancer and neurological diseases are caused due to excessive exposure or accumulation of metals like iron, zinc, and copper. The distribution of these elements is regulated by metal homeostasis, which is crucial for maintaining vital cellular functions, including oxygen transport, immune defense, and cellular energy management. The body retains metal homeostasis through mechanisms that control absorption, transport, and storage of these metals. When these regulatory processes malfunction, they give rise to disorders, such as hemochromatosis and Wilson's disease, which can lead to zinc deficiency. Notably, in neurodegenerative diseases like Alzheimer's and Parkinson's, disrupted metal regulation contributes to disease progression through inflammation, oxidative stress, and impaired molecular signalling, all of which aggravate neuronal damage and interfere with neurotransmitter activity. To better understand these mechanisms, researchers use animal models and virtual computer-based models to study how metal imbalance initiates and sustains disease states. Progress in treatment evaluation relies on transitioning from preclinical findings to clinical trials to assess both safety and effectiveness. Recently, computational tools have merged with personalized medicine, using computational software to develop innovative approaches for managing metal-related disorders. These studies focus on tracking biological mechanisms of metals and their links to brain damage, aiming to apply simulation strategies in future research on metal regulation.

Keywords: Animal models, Computational approaches, Inflammation, Metal dysregulation, Metal homeostasis, Neurotransmitter alteration, Neurodegenerative diseases, Oxidative stress, Preclinical studies, Personalized medicine.

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

Shamsher Singh (Eds.)

INTRODUCTION TO METAL DYSREGULATION

Metals are the naturally occurring elements that are typically solid, shiny, and excellent conductors of heat and electricity, such as iron, copper, and zinc. In the human body, certain metals known as essential trace elements are vital for biological functions like transporting oxygen, supporting immunity, healing, aiding brain development, and producing energy [1]. These metals are absorbed from food and carefully balanced through a system called metal homeostasis. When this regulation is disrupted, a condition known as metal dysregulation occurs, where the body may absorb too much, store too little, or misdirect these metals [2]. Such dysfunction can lead to serious health problems, including hemochromatosis, Wilson's disease, or zinc deficiency. In particular, disrupted metal balance in the brain has been linked to a wide range of illnesses, including cancer, developmental issues, and neurodegenerative diseases like Alzheimer's and Parkinson's, where excess metals contribute to oxidative stress, inflammation, and impaired nerve signaling, worsening brain damage over time [1].

BASIC TO METAL PHYSIOLOGY ROLE AND ITS CELLULAR UPTAKE

Cells require metal elements as essential components to carry out their vital functions. These metals are integrated into enzymes and hormones, which, in cooperation with proteins, activate key physiological processes [3]. For instance, iron plays a central role in oxygen transport *via* hemoglobin, zinc supports immune function and DNA synthesis, and copper is involved in energy metabolism and acts as an antioxidant [4]. To maintain proper metal levels, the body uses a regulated system involving transporters, sensors, and binding proteins [5]. These specialized transporters enable metals to enter cells; for example, iron is transported through the iron-transferrin complex, while zinc is taken in *via* ZIP and DMT1 transporters. Once inside the cell, metals are either used for metallic processes or stored in structures like mitochondria, where they also help in transporting metal-bound proteins [6]. However, if this regulation system fails, cells may experience metal imbalance, where either a deficiency or excess of metals leads to cellular dysfunction and potential damage.

Metal Dysregulation Targeting: Absorption, Transport, and Storage

The body regulates metal absorption, transport, and storage by using a precise system of control. The system contains important elements.

The gastrointestinal tract absorbs metals through mechanisms controlled by divalent metal transporter 1 (DMT1) and copper transporter 1 (CTR1) proteins, which facilitate uptake of iron and zinc or copper, respectively [7]. Normally, the

body controls the metal absorption rate to maintain stable homeostasis, increasing absorption during deficiencies and reducing it in conditions with metal surplus [8].

Metals circulating within the bloodstream are transported with the help of specific proteins: transferrin carries iron, albumin transports copper, and metallothioneins bind and transport zinc. These metal transport proteins not only carry metals but also protect them from causing damage during circulation by stabilizing their reactive nature. Once the metals reach their target tissues, they are either utilized immediately in cellular processes or stored for future metabolic needs, maintaining a balanced internal environment. The body stores excessive metals inside specific cells called hepatocytes, which place them in ferritin organelles (for iron) and metallothionein organelles (for copper and zinc) [9]. The stored substances protect cells from toxicity and serve as available reserves that the body activates during times of need.

Any dysfunction in the three metal metabolism processes (through genetics, environment, or diet) causes medical problems like hemochromatosis (excess iron), Wilson's disease (excess copper), and zinc deficiency issues [10]. With a comprehensive knowledge of metal absorption rules, transport mechanisms, and storage regulations, we can prevent and manage diseases related to metal regulation disturbances [11]. Table **1** shows metal roles, transporters, storage sites, and diseases linked to dysregulation.

Table 1. Metal roles, transporters, storage sites, and diseases linked to dysregulation.

Metal	Role	Transporter/Binding Protein	Storage Site	Disease Linked to Dysregulation	References
Iron	Oxygen transport in hemoglobin	Transferrin, DMT1	Hepatocytes (ferritin)	Hemochromatosis (iron overload)	[12]
Zinc	Immune function, DNA synthesis	ZIP transporters, Metallothioneins	Hepatocytes (metallothionein)	Zinc deficiency, Alzheimer's disease	[13]
Copper	Energy metabolism, antioxidant role	CTR1, ATP7A	Hepatocytes (metallothionein)	Wilson's disease (copper overload)	[14]

CHAPTER 13

Treatment Options for Metal-associated CNS Toxicity: Clinical Trials and Translational Research

Ravina Kumari[1], Medha Bhalla[1], Ramandeep Kaur[1], Ritu Kainth[1], Kousik Maparu[2], Shamsher Singh[2] and **Ajay Singh Kushwah[1,*]**

[1] *Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India*

[2] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Metals are vital to human health, contributing to cellular structure, gene expression, enzymatic functions, neurotransmission, and antioxidant defense. However, dysregulation in metal homeostasis—caused by environmental, occupational, or biological factors—can lead to severe health issues, particularly neurodegenerative disorders like Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease. Essential biometals such as iron, zinc, copper, manganese, magnesium, and calcium are crucial for physiological balance, while their dysregulation is linked to oxidative stress, protein aggregation, and neurodegeneration. Toxic metals like aluminium, cadmium, lead, and mercury further exacerbate these effects by impairing immune and mitochondrial function. Research has increasingly focused on metal transport mechanisms in neurological disorders. Therapeutic interventions include chelating agents to remove excess metals and drugs targeting metal transporters to restore balance. While preclinical models show promise, challenges persist in translating findings to human therapies due to individual variability and disease complexity. Longitudinal studies emphasize the importance of tracking metal exposure over time to better understand disease progression. Preventive and therapeutic strategies also involve dietary regulation and supplementation with essential minerals, along with minimizing exposure to harmful metals, especially in occupational settings. Emerging approaches integrate multi-omics technologies—genomics, proteomics, and metabolomics—to understand the complex role of metals in disease. AI-driven diagnostics and nanomedicine further enhance precision in diagnosis and treatment. This multidisciplinary approach highlights the need for continued research and collaboration to effectively address metal dysregulation and its implications for human health.

[*] **Corresponding author Ajay Singh Kushwah:** Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, India; E-mail: kushwah_ph05@yahoo.co.in

Shamsher Singh (Eds.)

Keywords: Alzheimer's disease (AD), Biometals, Chelating agents, Metal dysregulation, Neurodegenerative disorders.

INTRODUCTION

Metals are ubiquitous in our environment and enter the food chain through both natural and anthropogenic routes. Food is the major route of exposure to essential and nonessential metals. Essential metals such as iron, zinc, and magnesium play important roles in biochemical reactions, enzyme function, oxygen transport, and cellular signaling. Excessive consumption of even essential metals, however, leads to health problems like kidney damage, neuropsychiatric manifestations, and cardiovascular diseases. Heavy metals such as lead, cadmium, and mercury are highly toxic and can cause serious health hazards, including neurological impairment, renal failure, and increased cancer risk, at low exposure levels. Contamination of food with these metals results in acute effects of nausea and organ failure, as well as chronic effects like Alzheimer's disease, ADHD, autism, kidney disease, and cardiovascular diseases. These effects are mediated by oxidative stress, inflammation, endothelial dysfunction, and compromised immune system function [1].

Regulations on the presence of heavy metals in food are essential to protect public health. The primary metals of concern are lead, cadmium, mercury, and arsenic (a metalloid). To evaluate heavy metal content, reference values establish maximum levels (ML) for these metals in food. Regulation (EU) 2023/915 of the European Commission establishes rigorous ML levels for poisons so that they are as low as possible, based on good agricultural, fishery, and manufacturing practices [2]. The ML levels for lead and cadmium were most recently revised in 2021, and that for mercury and arsenic were revised in 2022 and 2023, respectively. Food business operators must implement measures to reduce contamination. The FAO and WHO's Codex Committee on Contaminants in Foods, released in 2017, also establishes ML values for quality factors such as tin, copper, iron, and zinc, and offers toxicological guidance values including the provisional tolerable weekly intake (PTWI), provisional tolerable monthly intake (PTMI), and benchmark dose (BMDL 0.5) values, which are given in micrograms per kilogram of body weight. Regulatory organizations such as the EPA, ATSDR, and JECFA set reference values to establish a safe level of heavy metal exposure [3]. These values, incorporated into the Heavy Metals Screening Tool (HMST), compare the intake of metals observed in humans and animals and aid in the evaluation of the safety of metal intake.

CURRENT RESEARCH LANDSCAPE ON METAL DYSREGULATION

Heavy metals, which include lead, cadmium, mercury, arsenic, and chromium, are another group of harmful environmental pollutants found in air, water, soil, food, and industrial products. Epidemiological studies have linked exposure to these metals with cardiovascular diseases due to increased generation of reactive oxygen species (ROS), leading to inflammation, endothelial dysfunction, disrupted lipid metabolism, and ion imbalances. Exposure to heavy metals increases the risk of hypertension, arrhythmia, and atherosclerosis. Public health measures, including chelation therapy, antioxidants such as vitamins and beta-carotene, and minerals including selenium and zinc, can assist in reducing the risk of cardiovascular incidences associated with heavy metal exposure [4].

Many researchers are exploring the toxic metal hypothesis, focusing on studies examining the distribution of toxic metals in the human brain, particularly through autometallography (AMG™). The evidence links exposure to metals like mercury, silver, and bismuth to neurological disorders. Cases of exposure include a man with continuous mercury exposure, a fisherman with intermittent mercury intake from fish, and a man with unknown silver exposure, all showing metals in brain regions such as the locus ceruleus. These findings suggest that toxic metals contribute to various disorders, such as MS, ALS, PD, and AD, with overlapping clinical features. Common brain cells affected include neurons, astrocytes, and oligodendrocytes. Additionally, exposure to metals may exacerbate conditions through mechanisms like inflammation, oxidative stress, and apoptosis (Table **1**) [5].

CLINICAL TRIAL AND TRANSLATIONAL RESEARCH

Trial Outcomes and Clinical Background

Metal ion competition for protein-binding sites can interfere with the movement of vital molecules and alter bodily chemical reactions. Many biological functions depend on metal ions, such as calcium and magnesium. However, because they can imitate or replace important metals at specific protein locations, other metals like lead and cadmium can obstruct these activities. This can cause toxicity and interfere with regular function. The capacity of a protein to bind particular metal ions over others is known as metal selectivity. But since every protein has different preferences for metal binding, researching proteins separately is necessary to comprehend how this functions. Understanding how proteins and metal ions interact is essential to comprehending the effects of heavy metals on human health. In particular, metal-mediated protein-protein interactions are a crucial field of research in this regard [14].

CHAPTER 14

Metal Imaging and Detection Techniques

Sudarshan Kumar[1], Pavittar Singh[1], Shamsher Singh[2] and **Vivek Asati[1,*]**

[1] *Department of Pharmaceutical Analysis, ISF College of Pharmacy, Moga, Punjab, India*

[2] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Metal imaging techniques are used in various scientific and clinical investigations, which help in the distribution and quantification of metal in biological samples. Different body processes of human beings require essential metals, including magnesium, calcium, iron, manganese, and zinc, but their improper ratios can result in multiple severe health complications, including cancer and metabolic disorders, along with neurodegeneration. This chapter covers the different techniques used for the detection of metals from biological samples, such as Atomic Absorption Spectroscopy (AAS), Inductively Coupled Plasma Mass Spectrometry (ICP-MS), X-ray Fluorescence (XRF), Neutron Activation Analysis (NAA), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET). The analysis evaluates these techniques based on principles of operation alongside their respective applications, benefits, and downsides in biological and environmental investigations. PET imaging serves three important healthcare fields by implementing metal-based radiotracers, which enhance accuracy in medical imaging processes. The deep-tissue analysis of metal ions becomes possible with MRI systems, although ICP-MS stands out for its ability to analyze biological samples containing trace metals at high speed. This chapter also addresses the various challenges faced by these techniques in the detection of metal from biological samples. This chapter provides a comprehensive study of metal detection methods and their future measurement trends.

Keywords: Atomic absorption spectroscopy, Magnetic resonance imaging, Metal imaging techniques, Neutron activation analysis, Positron emission tomography, X-ray fluorescence.

INTRODUCTION TO METAL DETECTION IN THE BIOLOGICAL SYSTEM

Metal is one of the vital components of plants, animals, and humans. For the maintenance of life, metal is required as one of the critical components;

* **Corresponding author Vivek Asati:** Department of Pharmaceutical Analysis, ISF College of Pharmacy, Moga, Punjab, India; E-mail: Vivekasatipharma47@gmail.com

Shamsher Singh (Eds.)

its absence can lead to several diseases, including retardation of growth, carcinogenicity, malfunctioning, and death [1]. Metals like magnesium (Mg), calcium (Ca), iron (Fe), manganese (Mn), and zinc (Zn) are the essential elements involved in energy production and the DNA repairing process, which play integral roles in sustaining life [2]. An imbalance of metal homeostasis can lead to the toxicity or deficiency of metal, which produces effects on human health such as anemia, neurodegeneration, and metabolic disorders [3]. Metal ions present in biological systems can be detected from various metal imaging techniques like atomic absorption spectroscopy (AAS), MRI (Magnetic Resonance Imaging), ICP-MS (Inductively Coupled Plasma Mass Spectrometry), NAA (Neutron Activation Analysis), CT-Scan (Computed Tomography), and PET-Scan (Positron Emission Tomography) [1, 4 - 8]. Different analytical techniques used for metal detection and analysis are represented in Fig. (**1**).

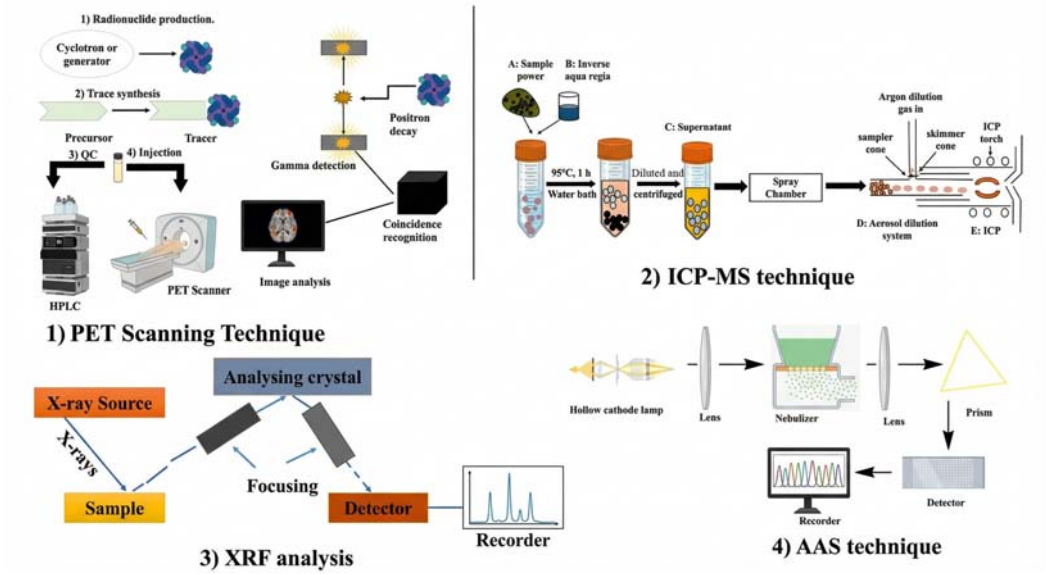

Fig. (1). The schematic view of different analytical techniques used for metal detection and analysis.

ATOMIC ABSORPTION SPECTROSCOPY (AAS)

AAS is a spectroscopic technique used to measure chemical element quantities in environmental samples by measuring the absorbent radiation of a compound of interest [9]. In 1955, Alan Wash developed the concept of atomic absorption for quantitative analysis [10]. The first commercial AAS instruments were developed by Perkin-Elmer [11]. AAS is based on the principle that free atoms in the ground state absorb light at specific wavelengths characteristic of their element. The amount of absorbed light is proportional to the concentration of the component of

the sample [12]. The AAS consists of a radiation source, an atomizer, a monochromator, a detector, and an amplifier. The major radiation sources are hollow cathode lamps, electrode discharge lamps, Xenon arc lamps, and deuterium lamps. The flame and electrochemical atomizers are the two main atomizers used to atomize the sample. Monochromators are used to select the specific wavelength absorbed by the analytes and remove unwanted radiation. Detectors like photomultiplier tubes (PMTs) and charged coupled detectors (CCDs) are used to measure the intensity of light. Atomization of AAS is the first step of AAS in which the analyte is converted into gaseous atoms by vaporizing a metal-containing solution in a flame. In this absorption process, ground-state atoms absorb energy, which causes an electronic transition that produces an atomic absorption spectrum. The absorbed light is converted into an electric signal, which is detected by a photomultiplier tube [13]. AAS is used in different applications, including environmental analysis, clinical and biomedical applications, food and agriculture, metallurgy, metal science, forensic science, industrial applications, archaeology, geology, and cosmetic and personal care [14 - 19]. AAS is widely used for trace metal analysis in biological fluids such as blood, plasma, urine, saliva, and sweat. This analysis helps diagnose disease, monitor nutritional deficiencies, and detect toxic metal exposure [20]. Different types of AAS techniques, like flame atomic absorption spectrometry, cloud point extraction, and electrochemical AAS, are used to extract metals present in biological samples. The FAAS technique uses coprecipitation for the detection of metals like Cr(III), Cu(II), Fe(III), Pb(II), Pd(II), and Zn(II) [21]. AAS also plays an important role in preclinical studies for the quantification of trace elements in pharmaceutical compounds. AAS is mainly used to measure the toxicity level of elements like lead (Pb), cadmium (Cd), and mercury (Hg) [22]. AAS in pre-clinical studies provides precise quantification of heavy metals from biological samples. In a recent study, AAS was used for the determination of cadmium and lead from mouse samples.

MRI (MAGNETIC RESONANCE IMAGING)

MRI is a non-penetrating technique that captures the image of internal structures and other bodily functions. In the presence of a magnetic field, electromagnetic and radio frequency radiation are used to capture the cross-sectional image of the body in any plane. This MRI technique has progressed over 30 years from being a technique with great potential to one that has become the primary diagnostic investigation for many clinical problems [23]. MRI works on the principle of a strong magnetic field aligned with hydrogen atoms in the body. Radio waves are used to disturb these atoms, and when they return to their original state, they release signals. After that, the computer processes these signals to create detailed images of organs and tissues [24]. MRI is used in diagnosing and monitoring

CHAPTER 15

Role of Nanotechnology as a Treatment Option for Neurodegenerative Disorders

Rajesh Kumar[1], Balwinder Kaur[2], Subhash Chand[3], Dhruva Kumar[4], Lovekesh Singh[5] and **Shamsher Singh[5,*]**

[1] *Department of Chemistry, Govt. Degree College Khundian, District Kangra, HP, India*

[2] *Department of Chemistry, Punjabi University, Patiala, Punjab, India*

[3] *Department of Chemistry, Lajpat Rai D.A.V College, Jagraon, Punjab, India*

[4] *Department of Chemistry, Guru Nanak College, Budhlada, Punjab, India*

[5] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: In today's fast-moving era of technology and science, nanotechnology has massive potential in treating various neurological disorders, particularly those caused by metals, such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis. These disorders are often accompanied by the accumulation or dysregulation of metals (*e.g*., aluminum, copper, iron, *etc*.) or metal-based toxic substances in the human brain, which can lead to neurotoxicity and neurodegeneration. The exceptional properties of nanomaterials, such as elevated surface area, improved reactivity, and their ability to traverse biological barriers, make them promising candidates for targeted therapeutic interventions. This chapter investigates the potential applications of nanotechnology in reducing the neurotoxic effects of metals. Here, some feasible future interventions using nanotechnology to provide novel strategies for early-stage diagnosis, personalized treatments, and long-term management of metal-related neurological disorders will be discussed. The incorporation of nanotechnology into clinical practice holds great promise for considerably improving patient outcomes and advancing the field of neurotherapeutics.

Keywords: Metal nanoparticles, Nanomaterials, Nanomedicine, Nanoparticle drug delivery, Nanotechnology, Neurological disorders, Neurotoxicity.

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

Shamsher Singh (Eds.)

INTRODUCTION TO NANOTECHNOLOGY

Brief History and Its Relevance in Healthcare

The term "nanotechnology" was introduced by Japanese scientist Norio Taniguchi in 1974 [1]. He utilized this term to refer to the meticulous fabrication of materials at the atomic and molecular levels, with a particular emphasis on creating ultraprecise surfaces. Nanotechnology is a field of science and engineering in which atoms and molecules are manipulated to design and create materials, structures, devices, and systems at the nanometer scale (*i.e.,* size between 1 and 100 nanometers) in at least one dimension [2]. To put it into perspective, one nanometer (nm) equals one-billionth of a meter, which is many orders of magnitude smaller than the width of a human hair, which is about 80,000 to 100,000 nm wide. Nanomaterials have unique physical, chemical, and biological properties that are beyond those of their macroscale counterparts, making them ideal for applications across several fields, including engineering, medicine, physics, chemistry, biology, and materials science [3 - 6]. This is because at this level, the behavior of atoms and molecules is primarily determined by quantum effects. Nanotechnology intends to manipulate and control matter at the atomic and molecular scales to create new materials and devices with groundbreaking properties. Nanotechnology is the engineering of functional systems at the molecular scale.

The history of nanotechnology in healthcare is rich and goes back a few decades with the evolution of advancements in materials science, molecular biology, and engineering. In the 1980s, Dr. K. Eric Drexler wrote the book "Engines of Creation" (1986), which made nanotechnology trendy [7]. Drexler wrote about creating molecular machines and assemblers that could be used for a variety of purposes, including healthcare. At the same time, progress in the engineering of nanomaterials like carbon nanotubes and nanoparticles was becoming increasingly promising for medical applications. Investigation of their potential for drug delivery systems, imaging, and diagnostic applications followed. By the 1990s, nanotechnology had made tangible advancements in the field of healthcare, particularly in the area of drug delivery. The development of liposomes, which are small microsomes made of lipid and can encapsulate drugs and transport them more specifically to target cells, provided a noteworthy breakthrough in drug formulation. In medicine, liposomal formulations for cancer chemotherapy, such as Doxil (FDA approved in 1995), were among the first clinical applications of nanotechnology. Nanotechnology has increasingly influenced medical imaging. The Food and Drug Administration (FDA) approved the first contrast agent for magnetic resonance imaging (MRI) in 1996, which utilized nanoparticles to improve image quality and provide improved

visualization of target tissues. By 2004, researchers from the Massachusetts Institute of Technology (MIT) had created "nanoparticle-based drug delivery systems" capable of targeting specific cells, such as cancer cells, with greater precision. This significant development set the stage for future progress in personalized medicine and target therapies. By the 2010s, numerous nanotechnology-based medicines *(i.e.*, nanomedicines) had been developed and were undergoing clinical trials. The FDA approved more treatments based on nanotechnology, such as Abraxane, a nanodrug used during the treatment of pancreatic and breast cancer. Likewise, nanotechnology has started to find applications in regenerative medicine, tissue engineering, and even vaccine development. Nanotechnology-based vaccines, such as mRNA vaccines, use lipid nanoparticles for delivering genetic material to cells [8]. The development and implementation of COVID-19 vaccines in the year 2020 also showcased the remarkable potential of nanotechnology to transform public health. Nanotechnology has been finding its way into various parts of healthcare during the 2020s, including drug delivery systems, gene therapies, medical imaging, tissue engineering, and precision medicine [9 - 12]. Nanorobots intended to assist minimally invasive surgeries and deliver drugs at the molecular level are the latest hope in this field. Nanotechnology has found a wide range of applications in diagnostics, from wearable devices that monitor health indicators to diagnostic sensors that detect diseases in their very early stages. Another area where nanomedicine is advancing is personalized medicine, where nanotechnology can be customized for individual patients to provide more targeted and effective care (Fig. **1**) [13].

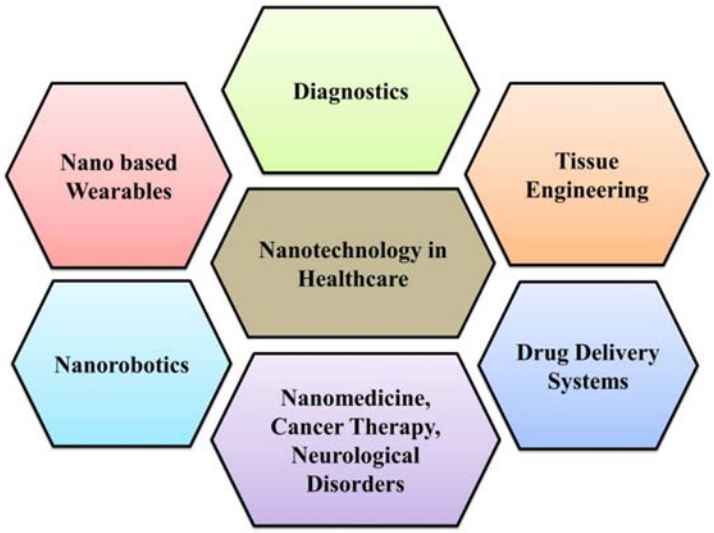

Fig. (1). Relevance of nanotechnology in healthcare.

CHAPTER 16

Lifestyle Management and Exercise as a Tool to Overcome Neurodegenerative Disorders

Lovekesh Singh[1], G.D. Gupta[2], Dhrita Chatterjee[1] and **Shamsher Singh[1,*]**

[1] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

[2] *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Metal homeostasis plays a critical role in maintaining physiological balance and preventing the onset of various chronic diseases. This chapter highlights the intricate relationship between essential trace metals- iron (Fe), zinc (Zn), and copper (Cu)- and lifestyle factors, including diet, physical activity, stress, sleep, smoking, and alcohol consumption. Disruptions in metal balance, often driven by poor lifestyle choices, have been linked to the development of neurodegenerative disorders, cardiovascular diseases, and cancer. Emerging evidence underscores the role of stress-induced hormonal changes and oxidative stress in metal dysregulation. Interventions such as meditation and exercise have been shown to mitigate oxidative burden, reduce inflammation, and support effective detoxification pathways, particularly through improved liver and kidney function. Furthermore, sleep quality and circadian rhythm synchronization contribute significantly to brain metal detoxification, with melatonin serving as a key neuroprotective agent. This chapter advocated for a holistic, prevention-oriented approach that integrated nutrition, physical activity, stress management, and sleep hygiene to maintain optimal metal homeostasis. Understanding the dynamic interplay between lifestyle behaviors and metal regulation may offer novel therapeutic strategies for managing metal-related pathologies and improving long-term health outcomes.

Keywords: Circadian rhythm, Exercise, Lifestyle management, Meditation, Melatonin, Metal dysregulation, Metal homeostasis, Oxidative stress, Stress management.

[*] **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

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INTRODUCTION TO LIFESTYLE MANAGEMENT

Lifestyle management is closely linked to the principles of health promotion, which is defined as "the process of enabling people to increase control over and improve their health [1]." Lifestyle management programs are structured health promotion services that guide individuals in adopting healthier behaviors, reducing health risks, and improving overall well-being [2]. These programs focus on managing medical conditions by addressing physical activity, stress, smoking cessation, and dietary practices [3]. While these initiatives can be found in various settings, they are particularly prominent in workplaces and public health programs [4].

IMPACT OF LIFESTYLE ON METAL HOMEOSTASIS

Essential metals such as iron, zinc, and copper are vital to numerous physiological functions. However, their absorption, distribution, and excretion can be significantly influenced by lifestyle factors, including diet, physical activity, stress, smoking, and alcohol consumption [5]. Poor nutrition, excessive intake of processed foods, and nutrient deficiencies can lead to both metal toxicity and deficiency. For example, intense physical activity may increase iron requirements and result in metal loss through sweating [6]. Chronic stress alters hormonal responses and promotes oxidative stress, disrupting metal metabolism. Tobacco introduces cadmium into the body, while excessive alcohol use impairs metal absorption and damages the liver, further affecting metal balance [7].

Metal imbalances can contribute to serious health outcomes, including anemia, immune dysfunction, nausea, organ damage, and increased risks for neurodegenerative, cardiovascular diseases, and cancer [8, 9]. Individual genetic makeup and environmental exposure to heavy metals also play a critical role in determining one's ability to maintain metal homeostasis [10].

Esther Ogundipe utilized data from the 2017–2018 National Health and Nutrition Examination Survey (NHANES) in her research approach. NHANES represents a cross-sectional survey developed by the U.S. Centers for Disease Control and Prevention (CDC) to assess nutritional and health indicators among a comprehensive national sample of non-institutionalized U.S. citizens. The survey adopts a multi-stage stratified sampling framework that gathers data in two-year cycles by recruiting participants from all 50 states and the District of Columbia. All participants were granted permission to be included before undergoing physical evaluations, during which researchers conducted interviews. Laboratories conducted blood sample analysis, while demographic information, including age, sex, and ethnicity, was collected through a CAPI system, which supported precise data entry. The Institutional Review Board at the National Center for Health

Statistics (NCHS) approved the study protocols to maintain ethical data collection standards for the whole process [7].

Another study, conducted by Ashish Sriram Mishra, highlights the urgent need for prevention-focused public health strategies as global rates of dementia and Alzheimer's disease continue to rise in the absence of a definitive cure. The research delves into various contributing factors, including genetic predispositions, vascular and metabolic disorders, and lifestyle behaviors, all of which collectively influence the onset of these conditions. Emphasizing the importance of early intervention, the study advocates for a holistic wellness approach, as attempts to mitigate individual risk factors in isolation have yielded inconsistent outcomes. Drawing on findings from European trials and observational studies, the research explores preventive strategies tailored to older adults across varying risk levels. Moreover, current pharmaceutical research is increasingly shifting toward pre-symptomatic intervention, aiming to prevent AD before cognitive decline becomes apparent. This study serves as a comprehensive resource, synthesizing insights from ongoing research to offer a thorough understanding of present and emerging preventive strategies against dementia and AD [11].

STRESS MANAGEMENT/MEDITATION

Chronic Stress and Metal Imbalance

Chronic stress impairs the body's ability to maintain proper metal balance. This happens because stress leads to hormonal changes and increased oxidative stress, which in turn causes imbalances in essential metals within the body [11]. One of the most affected balances is between zinc and copper, an imbalance that can significantly harm overall health. To counter this, methods that reduce metal-induced oxidative stress, control inflammation, and manage stress are important [12]. Practices such as meditation and stress management techniques have been shown to lower oxidative stress while also reducing inflammation. These benefits help maintain proper metal homeostasis in the body [13]. When individuals meditate, their bodies enter a relaxed state, cortisol levels decrease, and mental well-being improves [14]. All these factors support the body's natural regulatory processes. Effective stress management can therefore help prevent or reduce disruptions in the regulation of metals in the body [15]. Over time, this can lower health risks associated with both toxic metal build-up and deficiencies.

The research by Sonu Das revealed higher plasma measurements of iron and copper in COPD patients versus healthy adults, also showing parallel cadmium patterns. Research showed that COPD patients displayed elevated OSI levels from elevated TOS/TAS ratios, and these OSI measurements shared positive

CHAPTER 17

Research Directions and Future Perspectives

Kousik Maparu[1], Dhrita Chatterjee[1], Romanpreet Kaur[1] and **Shamsher Singh[1,*]**

[1] *Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India*

Abstract: Metals play a crucial role in neurological health, but their dysregulation is increasingly linked to neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's. This section explores future research directions focusing on the mechanisms of metal-induced neurotoxicity, including oxidative stress, protein aggregation, and receptor dysregulation. Advanced multi-omics approaches and systems biology are vital for identifying disease-specific metal signatures and therapeutic targets. The development of sensitive diagnostics, such as metal-specific imaging agents and biosensors, can enhance early detection and treatment monitoring. Nanotechnology and targeted drug delivery systems offer promising strategies to modulate metal homeostasis across the blood-brain barrier. Artificial intelligence and personalized medicine are emerging as powerful tools to predict disease progression based on metal exposure and genetic factors. Finally, addressing environmental and occupational exposures through longitudinal studies and regulatory policies remains essential. A multidisciplinary approach is critical to advancing diagnostic therapeutics and prevention strategies in metal-related neurological disorders.

Keywords: Artificial intelligence, Multi-omics study, Nanotechnology , Personalized medicine, Targeted drug delivery system.

INTRODUCTION

Understanding the intricate relationship between metals and neurological disorders is a rapidly evolving field. Future research must delve deeper into the molecular mechanisms by which both essential and toxic metals influence neurotoxicity, receptor modulation, and disease progression. The role of metals in neurological disorders is increasingly recognized as a critical area of biomedical research, particularly due to their involvement in oxidative stress, neuroinflammation, protein aggregation, and mitochondrial dysfunction. Although significant advances have been made in understanding how essential and toxic

* **Corresponding author Shamsher Singh:** Neuropharmacology Division, Department of Pharmacology, ISF College of Pharmacy, Moga, Punjab, India; E-mail: shamshersinghbajwa@gmail.com

Shamsher Singh (Eds.)

metals contribute to neurodegenerative processes, numerous gaps remain in our mechanistic understanding and translational applications. Addressing these gaps requires a concerted effort to integrate molecular biology, toxicology, pharmacology, bioinformatics, and clinical sciences. Emerging technologies such as multi-omics approaches, integrating genomics, transcriptomics, metabolomics, and proteomics, hold immense potential for elucidating complex metal-disease interactions. These tools can uncover biomarkers of early neurodegeneration linked to metal exposure and assist in identifying patient-specific therapeutic targets. AI-powered diagnostics and predictive models offer a promising avenue for assessing individual risk and tailoring interventions based on metal exposure profiles and genetic predispositions. Therapeutically, future strategies should be focused on targeted drug development, including metal chelators with enhanced blood-brain barrier permeability, and drugs that selectively modulate metal-dependent receptor activity. Additionally, nanomedicine offers innovative solutions for the precise delivery of metal-regulating agents to affected brain regions. A multidisciplinary, collaborative research framework will be essential to translate laboratory findings into clinically effective strategies for preventing and managing metal-associated neurodegenerative disorders.

MECHANISTIC INSIGHTS INTO METAL-INDUCED NEUROTOXICITY

Future research should prioritize dissecting the precise molecular pathways through which metals exert neurotoxic and neuroprotective effects. For instance, elucidating how iron, copper, and zinc dysregulation promote tau phosphorylation, amyloid beta aggregation, and alpha-synuclein toxicity will shed light on early pathogenic events in Alzheimer's and Parkinson's diseases. Investigating how metals alter receptor signaling, like NMDA, AMPA, and dopamine receptors, will further clarify their impact on synaptic transmission and neuroplasticity. Moreover, understanding how toxic metals like lead, mercury, and cadmium disrupt mitochondrial respiration, impair calcium signaling, and induce chronic inflammation may identify novel intervention points. These mechanistic insights will be vital for developing targeted therapeutics that not only restore metal balance but also mitigate downstream effects of dysregulation.

ADVANCEMENTS IN OMICS AND SYSTEMS BIOLOGY

Multi-omics approaches, including genomics, transcriptomics, proteomics, metabolomics, and metallomics, are revolutionizing the way we study metal interaction in the nervous system. These tools allow researchers to map complex networks involving metal transporters, storage proteins, redox enzymes, and signaling molecules. Systems biology models integrating omics data can provide holistic views of metal-driven pathology and help identify critical nodes for

therapeutic targeting. Further research is needed to construct metal-specific disease signatures that can differentiate between early and advanced stages of neurodegenerative disorders. Integration with neuroimaging and fluid biomarkers will improve the diagnosis, monitoring, and prognosis of metal-related neuropathologies.

DEVELOPMENT OF DIAGNOSTIC AND MONITORING TOOLS

Another promising direction involves the development of sensitive and specific diagnostic tools for detecting metal imbalance in the brain. Metal-specific PET-tracers, MRI contrast agents, and fluorescent probes can enable real-time visualization of metal accumulation and distribution *in vivo.* These technologies will be valuable not only for yearly diagnosis but also for monitoring treatment efficacy in clinical trials. Moreover, wearable biosensors and lab-on-a-chip platforms that detect metal levels in blood, urine, or cerebrospinal fluid offer non-invasive approaches for continuous exposure monitoring, especially in occupational or high-risk populations.

TARGETED THERAPIES AND DRUG-DELIVERY SYSTEMS

Despite the progress in identifying metal chelators and modulators of metal homeostasis, challenges persist in delivering these agents effectively across the blood-brain barrier (BBB). Future research should focus on designing brain-penetrant compounds that selectively target deregulated metal pools without disrupting physiological metal functions. Nanotechnology-based drug delivery systems, such as liposomes, dendrimers, and metal-binding nanoparticles, are promising tools for enhancing viability and specificity. Functionalization of these carriers with ligands or antibodies can facilitate targeted delivery to affected brain regions or cell types. Additionally, research into small molecule modulators of metal transporters, like as DMT1, ferroportin, and ATP7A/B, may lead to therapies that restore intracellular metal homeostasis. Gene editing technologies like CRISPR/Cas9 may also offer long-term solutions by correcting mutations in metal handling proteins, potentially helping to treat inherited neurodegenerative disorders.

PERSONALIZED MEDICINE AND AI INTEGRATION

The integration of artificial intelligence and machine learning into metal neurotoxicity offers new opportunities for data-driven discoveries. AI algorithms can process large-scale omics and environmental exposure datasets to identify patterns that may predict disease onset, progression, or treatment response. Personalized medicine approaches will benefit from AI-assisted risk assessment,

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Shamsher Singh

Shamsher Singh is presently working as Dean Research & Head, Department of Pharmacology, ISF College of Pharmacy, Moga, affiliated with IK Gujral Punjab Technical University Jalandhar, Punjab, India. He did his M. Pharm. and Ph. D. from ISFCP, Moga. He has been contributing dedicatedly to pharmaceutical education and research for the past several years. Dr. Singh is a prolific writer with more than 200 publications in various reputed peer-reviewed journals to his credit. Besides this, he has contributed 27 International book chapters related to experimental animal models in Springer Nature and 11 books and 11 granted design patents from the Government of India (Patent Office). He has guided more than 65 M. Pharm. (Pharmacology) and undergraduate students, as well as 8 Ph.D. scholars in the area of neurological disorders. Dr. Singh received 6 research projects worth 92 lakh and 05 travel grants from different government bodies (ICMR, DST, IBRO, MDS) in neurological areas. He received 7 research awards from Malaysia, Japan, and India, and was recognized among the top 2% of scientists in 2024 as per Elsevier data compiled by Stanford University, USA.